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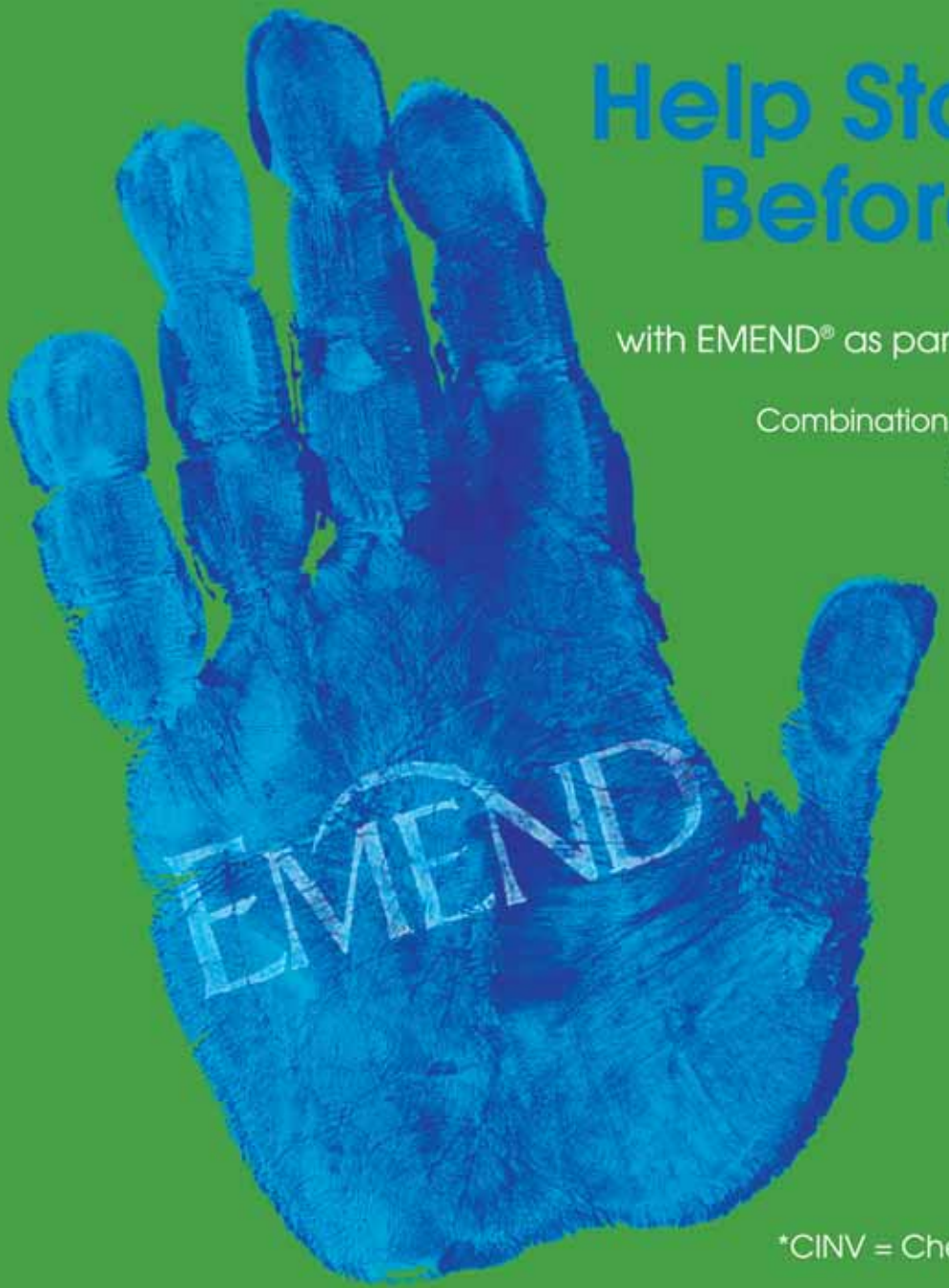

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2. Nolvadex®-D Aproved Package Insert
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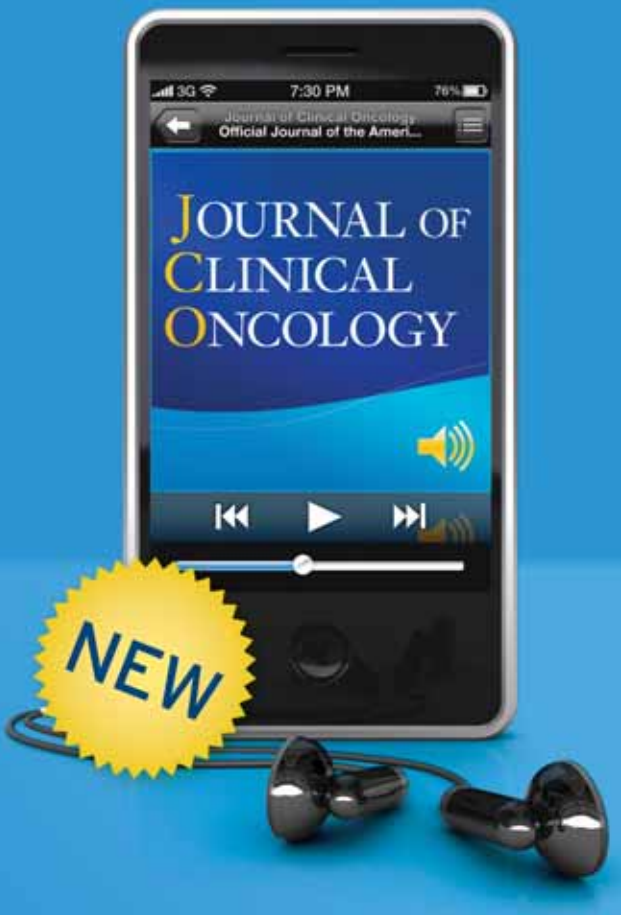

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JOURNAL OF CLINICAL ONCOLOGY

ORIGINAL REPORT

Dose-Intensification in Early Unfavorable Hodgkin's Lymphoma: Final Analysis of the German Hodgkin Study Group HD14 Trial

Bastian von Tresckow, Annette Plütschow, Michael Fuchs, Beate Klimm, Jana Markova, Andreas Lohri, Zdenek Kral, Richard Greil, Max S. Topp, Julia Meissner, Josée M. Zijlstra, Martin Soekler, Harald Stein, Hans T. Eich, Rolf P. Mueller, Volker Diehl, Peter Borchmann, and Andreas Engert

Processed as a Rapid Communication manuscript. See accompanying editorial on page 895; listen to the podcast by Dr Armitage at www.jco.org/podcasts

A B S T R A C T

Purpose
In patients with early unfavorable Hodgkin's lymphoma (HL), combined modality treatment with four cycles of ABVD (adriamycin, bleomycin, vinblastine, and dacarbazine) and 30 Gy involved-field radiotherapy (IFRT) results in long-term tumor control of approximately 80%. We aimed to improve these results using more intensive chemotherapy.

Patients and Methods
Patients with newly diagnosed early unfavorable HL were randomly assigned to either four cycles of ABVD or an intensified treatment consisting of two cycles of escalated BEACOPP (bleomycin, etoposide, adriamycin, cyclophosphamide, vincristine, procarbazine, and prednisone) followed by two cycles of ABVD (2 + 2). Chemotherapy was followed by 30 Gy IFRT in both arms. The primary end point was freedom from treatment failure (FFTF); secondary end points included progression-free survival (PFS) and treatment-related toxicity.

Results
With a total of 1,528 qualified patients included, the 2 + 2 regimen demonstrated superior FFTF compared with four cycles of ABVD ($P < .001$; hazard ratio, 0.44; 95% CI, 0.30 to 0.66), with a difference of 7.2% at 5 years (95% CI, 3.8 to 10.5). The difference in 5-year PFS was 6.2% (95% CI, 3.0% to 9.5%). There was more acute toxicity associated with 2 + 2 than with ABVD, but there were no overall differences in treatment-related mortality or secondary malignancies.

Conclusion
Intensified chemotherapy with two cycles of BEACOPP escalated followed by two cycles of ABVD followed by IFRT significantly improves tumor control in patients with early unfavorable HL.

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Bastian von Tresckow, Annette Plütschow, Michael Fuchs, Beate Klimm, Rolf P. Mueller, Volker Diehl, Peter Borchmann, and Andreas Engert, University of Cologne, Cologne; Max S. Topp, University of Wuerzburg, Wuerzburg; Julia Meissner, University of Heidelberg, Heidelberg; Martin Soekler, University of Tuebingen, Tuebingen; Harald Stein, University Hospital Benjamin Franklin Berlin, Berlin, Germany; Jana Markova, University Hospital Kralovske Vinohrady, Charles University Prague, Prague; Zdenek Kral, University Hospital of Brno, Brno, Czech Republic; Andreas Lohri, Cantonal Hospital, Liestal, Switzerland; Richard Greil, University of Salzburg, Salzburg, Austria; and Josée M. Zijlstra, Vrije Universiteit University Medical Centre Amsterdam, Amsterdam, the Netherlands.

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Supported by Grant No. 106164 from German Cancer Aid (Deutsche Krebshilfe) and the Swiss Federal Government. The German Hodgkin Study Group is a founding member of the Competence Network Malignant Lymphoma and has been granted partial support by the Federal Ministry for Education and Research (Bundesministerium für Bildung und Forschung) since 1999.

Presented in part at the 52nd Annual Meeting of the American Society of Hematology, December 4-7, 2010, Orlando, FL.

Authors' disclosures of potential conflicts of interest and author contributions are found at the end of this article.

Clinical Trials repository link available on JCO.org.

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INTRODUCTION

To date, the standard treatment of early unfavorable Hodgkin's lymphoma (HL) for most cooperative groups is combined modality treatment with four cycles of ABVD (adriamycin, bleomycin, vinblastine, and dacarbazine) and 30 Gy involved-field radiotherapy (IFRT).[1-3] This results in approximately 80% long-term tumor control, which is not satisfying when compared with results in early favorable HL.[4] Earlier attempts using BEACOPP (bleomycin, etoposide, adriamycin, cyclophosphamide, vincristine, procarbazine, and prednisone) in baseline dose did not improve results, as demonstrated in the GHSG (German Hodgkin Study Group) HD11 study.[5] On the basis of the high efficacy of BEACOPP escalated (BEACOPPesc) in advanced stages,[6,7] we decided to evaluate this dose-intensified regimen in early unfavorable HL. The randomized GHSG HD14 trial thus compared four cycles of ABVD (standard arm) with two cycles BEACOPPesc followed by two cycles of ABVD (2 + 2). Here we report the final results of this trial.

PATIENTS AND METHODS

The HD14 protocol was designed by the GHSG steering committee and approved by the ethics committees of participating centers (Data Supplement). An independent data safety committee monitored patient safety and efficacy of treatment throughout the study period. When the third planned interim analysis yielded a significant group

sequential test (adjusted overall $P = .0452$), the trial was stopped according to protocol. Randomization was discontinued on July 10, 2008, and the final analysis was scheduled so that all randomly assigned patients would have been followed for at least 1 year after final restaging.

Patients

Entry into the trial was restricted to patients with stage IA, IB, or IIA histologically proven HL with at least one of the following risk factors: bulky mediastinal mass (≥ one third maximum transverse thorax diameter); extranodal involvement; erythrocyte sedimentation rate (ESR) ≥ 50 mm/h (without B symptoms) or ESR ≥ 30 mm/h (with B symptoms); or three or more lymph node areas involved. Patients with stage IIB disease with either of the latter two risk factors were also included.

After initial diagnosis by the local pathologist, biopsy material was centrally reviewed by at least one member of a panel of six HL pathology experts. All patients provided written informed consent before study entry according to the Good Clinical Practice guidelines of the International Conference on Harmonisation and national regulations.

Study Design

Patients were recruited and treated in 407 hospitals and practices in Germany, Switzerland, the Netherlands, the Czech Republic, and Austria. After written informed consent and clinical staging, patients were registered at the GHSG central trial office by telephone and then randomly assigned at an allocation ratio of 1:1 to standard arm A with four cycles of ABVD or to the experimental arm B with 2 + 2 chemotherapy. Standard 30 Gy IFRT was administered as consolidation therapy in both arms. Stratification factors for randomization included participating center, age, constitutional symptoms, large mediastinal tumor or bulky disease, and supra- or infradiaphragmatic involvement.

Study Conduct

ABVD was administered at standard doses consisting of doxorubicin 25 mg/m^2 (days 1 and 15), bleomycin 10 mg/m^2 (days 1 and 15), vinblastine 6 mg/m^2 (days 1 and 15), and dacarbazine 375 mg/m^2 (days 1 and 15), repeated on day 29. Granulocyte colony-stimulating factor was administered if clinically indicated, starting from day 7 or 21. BEACOPPesc included cyclophosphamide 1,250 mg/m^2 (day 1), doxorubicin 35 mg/m^2 (day 1), etoposide 200 mg/m^2 (days 1 to 3), procarbazine 100 mg/m^2 (days 1 to 7), prednisone 40 mg/m^2 (days 1 to 14), vincristine 1.4 mg/m^2 (day 8; maximum, 2 mg), and bleomycin 10 mg/m^2 (day 8), repeated on day 22. Granulocyte colony-stimulating factor had to be administered from day 8 of each BEACOPPesc cycle until recovery of WBC to at least 1,000/μL on 3 consecutive days. Treatment was postponed until recovery of WBC to at least 2,500/μL and platelet count to at least 80,000/μL on the day scheduled for re-treatment. In cases of treatment postponement of more than 2 weeks or pronounced toxicity during treatment, dose reductions were foreseen in the trial protocol.

RT

On the basis of the initial staging, the expert RT panel provided an individual RT plan for each patient. All patients received 30 Gy IFRT in single fractions of 1.8 to 2.0 Gy administered five times per week.

End Points

The primary efficacy end point was freedom from treatment failure (FFTF); secondary end points included overall survival (OS), progression-free survival (PFS), response rates, and treatment-related toxicity.

Statistical Methods

This trial employed a two-arm parallel group design aimed at demonstrating superiority of the 2 + 2 regimen compared with four cycles of ABVD with respect to the primary end point of FFTF. To detect the need for early termination, a group sequential design with five interim analyses was planned.

Assessment of Treatment Effects

The trial was analyzed using group sequential methods[8-10] with appropriately adjusted CIs and P values for the primary end point of FFTF. Time-to-event end points were compared between groups using the Kaplan-Meier method and log-rank tests for P values as well as univariate Cox regression for hazard ratios (HRs). To detect a possible impact of prognostic factors, preplanned multivariate Cox regressions were performed as sensitivity analyses on the same analysis sets. Outcomes and toxicity rates were analyzed using Fisher's exact test. Design and analysis of the trial were carried out using SAS versions 8 to 9.2 (SAS Institute, Cary, NC) and ADDPLAN versions 3.1 to 5 (ADDPLAN, Cologne, Germany).

Analysis Sets

The full analysis set (FAS) consisted of all randomly assigned patients with confirmed histology. According to the trial protocol, patients with violations of major inclusion or exclusion criteria as well as withdrawals before start of therapy had to be excluded from the primary analysis set of qualified patients (QAS). Sensitivity analyses of efficacy end points were carried out on the FAS as well as on the per-protocol analysis set (PAS). Criteria to exclude patients from the PAS apart from violation of major inclusion or exclusion criteria were change of treatment arm, early treatment discontinuation, or relevant dose deviations of chemotherapy, unless resulting from death or progression.

RESULTS

Patients

Between January 2003 and July 2008, 1,655 patients with histologically confirmed early unfavorable HL were recruited (Fig 1). Because of insufficient documentation, 32 patients were excluded from all analyses. Therefore, the FAS comprised 1,623 patients; 818 were randomly assigned to arm A and 805 to arm B. Seven patients who withdrew from the trial before starting chemotherapy and 88 patients with major inclusion or exclusion criteria violations were excluded from the QAS, which was the main analysis set for the arm comparison and comprised 1,528 patients (765 in arm A; 763 in arm B). Because they did not receive the assigned treatment, or because adherence to protocol could not be confirmed, 97 QAS patients were excluded from the PAS.

Demographic baseline characteristics, stage of disease, and risk factors of patients were well balanced between treatment arms (Appendix Table A1, online only). In the QAS, 53.3% of patients were women. The median age was 32 years (range, 18 to 60 years); 9.4% were older than 50 years of age; 4.8% of patients had stage I disease (2.6% IA; 2.2% IB); 95.2% had stage II disease (67.5% IIA; 27.7% IIB). The most common risk factor was three or more involved lymph node areas (69.7%), followed by high ESR (52.9%), large mediastinal mass (18.7%), and extranodal involvement (8.1%). Localized infradiaphragmatic disease was present in 5.6% of patients.

A histologic review was performed in 86.4% of patients. The most frequent histologic subtypes were nodular sclerosis (70.3%) and mixed cellularity (18.2%).

Dose Delivery

As defined in the study protocol (Appendix Table A2, online only), 97.8% of evaluable QAS patients received four cycles of chemotherapy. In both arms, chemotherapy was administered according to protocol in most cases, with no difference between arms (relative total doses [± standard deviation] were 98.8 ± 4.7 and 97.6 ± 4.2 in arms A and B, respectively). Dose-intensity was also identical (0.9 ± 0.1).

Safety and Adverse Event Profiles

During chemotherapy, acute toxicity (WHO grade 3 to 4; Table 1) was significantly more frequent in arm B (87.1%) as compared with arm A (50.7%), with at least one grade 4 toxicity in 56.6% (arm B) and

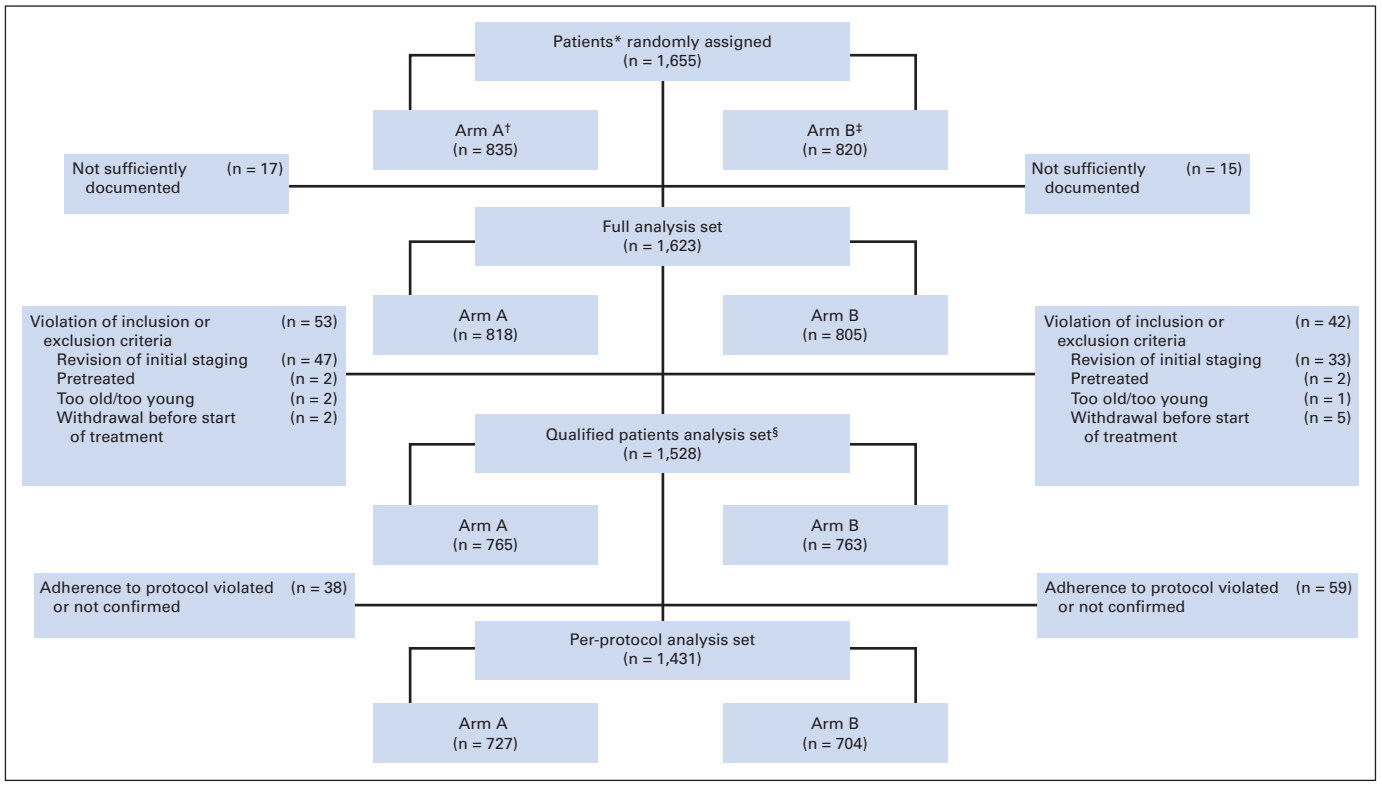

Fig 1. CONSORT diagram. (*) Patients were assessed for eligibility at individual trial centers, and histology was confirmed before registration and random assignment at the central trial office. (†) Arm A received four cycles of doxorubicin, bleomycin, vinblastine, and dacarbazine (ABVD) plus 30 Gy involved-field radiotherapy (IFRT). (‡) Arm B received two cycles of bleomycin, etoposide, doxorubicin, cyclophosphamide, vincristine, procarbazine, and prednisone, plus two cycles of ABVD plus 30 Gy IFRT. (§) The qualified patient analysis set is the primary analysis set according to the trial protocol.

5.9% (arm A), respectively. Four patients (0.52%) died as a result of acute toxicity in first-line therapy; all were treated in arm B. Most frequent toxicities were myelosuppression and hair loss in both arms. As expected, there was more acute toxicity associated with BEACOPPesc than with ABVD. Interestingly, there was also more toxicity associated with ABVD when administered after two cycles of BEACOPPesc than after two cycles of ABVD. The inclusion of non-qualified patients in a sensitivity analysis did not lead to additional findings on safety or feasibility (data not shown).

After a median follow-up of 43 months, 36 (2.4%) of 1,528 QAS patients had died (Table 2). The main reasons were secondary malignancies (n = 8), HL (n = 7), and toxicity of salvage therapy (n = 7). Overall, 32 secondary malignancies occurred in the QAS (arm A, 17 instances [2.2%]; arm B, 15 instances [2.0%]). Because of the low number of events, there were no statistically relevant differences in the total number of deaths or secondary neoplasms between treatment arms.

Efficacy

The overall complete response/unconfirmed complete response rate in the QAS was 95.4% (Appendix Table A3, online only), with no arm difference ($P = .6272$). With a median observation time of 43 months, the reported progression/relapse rate was 5.4% overall (Table 2), with 2.5% in arm B and 8.4% in arm A. More patients in arm A than in arm B had a second relapse (1.4% *v* 0.4%), but there were not enough events to yield a significant arm difference.

As shown in Figures 2A to 2C (and Appendix Table A4, online only), OS was 97.0% at 5 years (95% CI, 95.9% to 98.1%) and did not differ between treatment arms ($P = .7308$). For the primary end point of FFTF, superiority of arm B was established by a significant group sequential test in the third planned interim analysis, with an adjusted two-sided overall P value of .0451. In the final analysis, the nonadjusted P value was $< .001$ (HR, 0.44; 95% CI, 0.30 to 0.66). Five-year FFTF rates of 87.7% (95% CI, 84.8% to 90.6%) and 94.8% (95% CI, 93.1% to 96.6%) in arms A and B, respectively, resulted in a difference of 7.2% (95% CI, 3.8% to 10.5%). PFS was also significantly better in arm B on the adjusted 2.5% level (HR, 0.45; 95% CI, 0.30 to 0.69; $P < .001$). The difference in 5-year PFS rates was 6.2% (95% CI, 3.0% to 9.5%). Thus, superiority of arm B in terms of FFTF as well as PFS can be concluded. Prespecified sensitivity analyses performed on the FAS and PAS yielded similar results (Appendix Figs A1A to A1D, online only).

Of the 64 patients experiencing relapse or progression after four cycles of ABVD, 12 (19%) died. Median survival time after diagnosis of first progression or relapse was 15 months (range, 3.6 to 42.7 months). Sixteen survivors were lost to follow-up within 1 year after diagnosis of HL progression or relapse. Thirty-six patients underwent successful salvage therapy and had a median observation time after first progression or relapse of 34 months (range, 12.9 to 73.4 months). In the 2 + 2 arm, six (32%) of 19 patients died after first-line therapy failure. Their median survival time after diagnosis of first progression or relapse was 12 months (range, 1.2 to 22.4 months). Four survivors were lost to follow-up within 1 year after diagnosis of HL progression or relapse. Nine patients underwent successful salvage therapy and had a median observation time after first progression or relapse of 38 months (range, 15.0 to 60.6 months).

Table 1. Acute Toxicities of Chemotherapy

Toxicity‡	Treatment Arm*† A (n = 757) No. of Patients	A (n = 757) %	B (n = 744) No. of Patients	B (n = 744) %
At least one toxicity during treatment§	384 of 757	50.7	648 of 744	87.1
Chemotherapy cycle				
1	175 of 761	23.0	501 of 745	67.2
2	226 of 760	29.7	549 of 742	74.0
3	263 of 756	34.8	429 of 729	58.8
4	254 of 748	34.0	402 of 723	55.6
At least one hematologic toxicity during treatment§	182 of 757	24.0	597 of 744	80.2
Chemotherapy cycle				
1	92 of 761	12.1	433 of 745	58.1
2	86 of 760	11.3	468 of 742	63.1
3	84 of 756	11.1	273 of 729	37.4
4	80 of 748	10.7	244 of 723	33.7
Type of acute toxicity				
Anemia	7	0.9	67	9.0
Thrombopenia	1	0.1	163	21.9
Leukopenia	178	23.5	588	79.0
Nausea/vomiting	104	13.7	76	10.2
Mucositis	3	0.4	32	4.3
GI tract	14	1.8	43	5.8
Urogenital tract	2	0.3	0	0
Respiratory tract	11	1.5	13	1.7
Drug fever	6	0.8	17	2.3
Allergy	2	0.3	12	1.6
Heart	2	0.3	1	0.1
Hair	179	23.6	356	47.8
Infection	26	3.4	54	7.3
Skin	8	1.1	2	0.3
Pain	27	3.6	54	7.3
Nervous system	6	0.8	24	3.2

Abbreviations: ABVD, doxorubicin, bleomycin, vinblastine, and dacarbazine; BEACOPP, bleomycin, etoposide, doxorubicin, cyclophosphamide, vincristine, procarbazine, and prednisone; IFRT, involved-field radiotherapy.

*Of 1,528 qualified patients, 1,506 (arm A, 761; arm B, 745) were documented for acute toxicities for at least one cycle, and 1,501 (arm A, 757; arm B, 744) were documented for acute toxicities for all cycles administered. Patients were analyzed according to arm as treated.

†Arm A received four cycles of ABVD plus 30 Gy IFRT; arm B received two cycles of BEACOPP plus two cycles of ABVD plus 30 Gy IFRT.

‡Toxicity of WHO grade III or IV only.

§$P < .001$.

Prognostic Factors and Subgroup Analyses

The only significant ($P < .05$) predictors for PFS events in the univariate regression analysis were large mediastinal mass and elevated ESR. Other factors such as extranodal disease, more than two involved regions, infradiaphragmatic disease, B symptoms, sex, and age were not significant. In a multivariate model for PFS including all these factors as well as treatment arm, the same two risk factors and treatment arm were significant, with estimated HRs of 2.4 (large mediastinal mass), 2.1 (elevated ESR), and 2.3 (arm A). In posthoc subgroup analyses of the FAS, patients with at least one of the two significant risk factors (high-risk group [n = 1,013]; 81 failure events for PFS) were compared with patients without any of these risk factors (low-risk group [n = 610]; 25 failure events). Five-year PFS was 94.0% (95% CI, 91.3% to 96.7%) in the low-risk group, compared with 91.2% (95% CI, 89.3% to 93.2%) in the high-risk group. The inferiority of the high-risk group was more pronounced for patients in arm A ($P = .0072$) than in arm B ($P = .1071$), but it should be noted that there was not enough power to detect an interaction between treatment arm and risk group (Appendix Figs A2A to A2D, online only). A subgroup analysis with large mediastinal mass and stage IIB as risk factors demonstrated similar results (Appendix Figs A3A, A3B, online only).

DISCUSSION

The GHSG HD14 trial compared intensified chemotherapy consisting of two cycles of BEACOPPesc followed by two cycles of ABVD (2 + 2) with the previous standard of four cycles of ABVD to improve tumor control in patients with early unfavorable HL. All patients received 30 Gy IFRT after chemotherapy. The intensified 2 + 2 arm was clearly superior in terms of FFTF and PFS, despite moderately higher acute toxicity.

In contrast to significant improvements in early favorable and advanced stage HL,[4,6] no significant progress has recently been reported for early unfavorable HL. More aggressive regimens such as BEACOPP baseline were evaluated, but neither the EORTC (European Organisation for Research and Treatment of Cancer) H9-U

Table 2. Failure Events and Late Effects*

Event/Effect	Treatment Arm† A (n = 765) No. of Patients	%	B (n = 763) No. of Patients	%
Death resulting from:‡	17	2.2	19	2.5
HL	3		4	
Toxicity of study chemotherapy	0		4	
Toxicity of salvage therapy	6		1	
Secondary neoplasia	5		3	
Suicide	1		0	
Respiratory	0		2	
Brain	0		1	
Other disease	1		3	
Unclear	1		1	
Progression or first relapse§	64	8.4	19	2.5
Progression	23	3.0	6	0.8
Early relapse	23	3.0	7	0.9
Late relapse	18	2.4	6	0.8
Second relapse‖	11		3	
Secondary malignancy¶	17	2.2	15	2.0
AML/MDS	0		2	
NHL	9		5	
Solid tumor	8		8	

Abbreviations: ABVD, doxorubicin, bleomycin, vinblastine, and dacarbazine; AML, acute myeloid leukemia; BEACOPP, bleomycin, etoposide, doxorubicin, cyclophosphamide, vincristine, procarbazine, and prednisone; FAS, full analysis set; HL, Hodgkin's lymphoma; IFRT, involved-field radiotherapy; MDS, myelodysplastic syndrome; NHL, non-Hodgkin's lymphoma.

*Median observation time, 43 months (95% CI, 41.5 to 43.6).

†Total of 1,528 qualified patients were analyzed according to arm as randomly assigned. Arm A received four cycles of ABVD plus 30 Gy IFRT; arm B received two cycles of BEACOPP plus two cycles of ABVD plus 30 Gy IFRT.

‡Four additional patients in the FAS who were not qualified died as a result of second malignancy (n = 2) and HL (n = 2).

§$P < .001$.

‖$P = .0563$.

¶Three nonqualified patients in the FAS also had a secondary neoplasm.

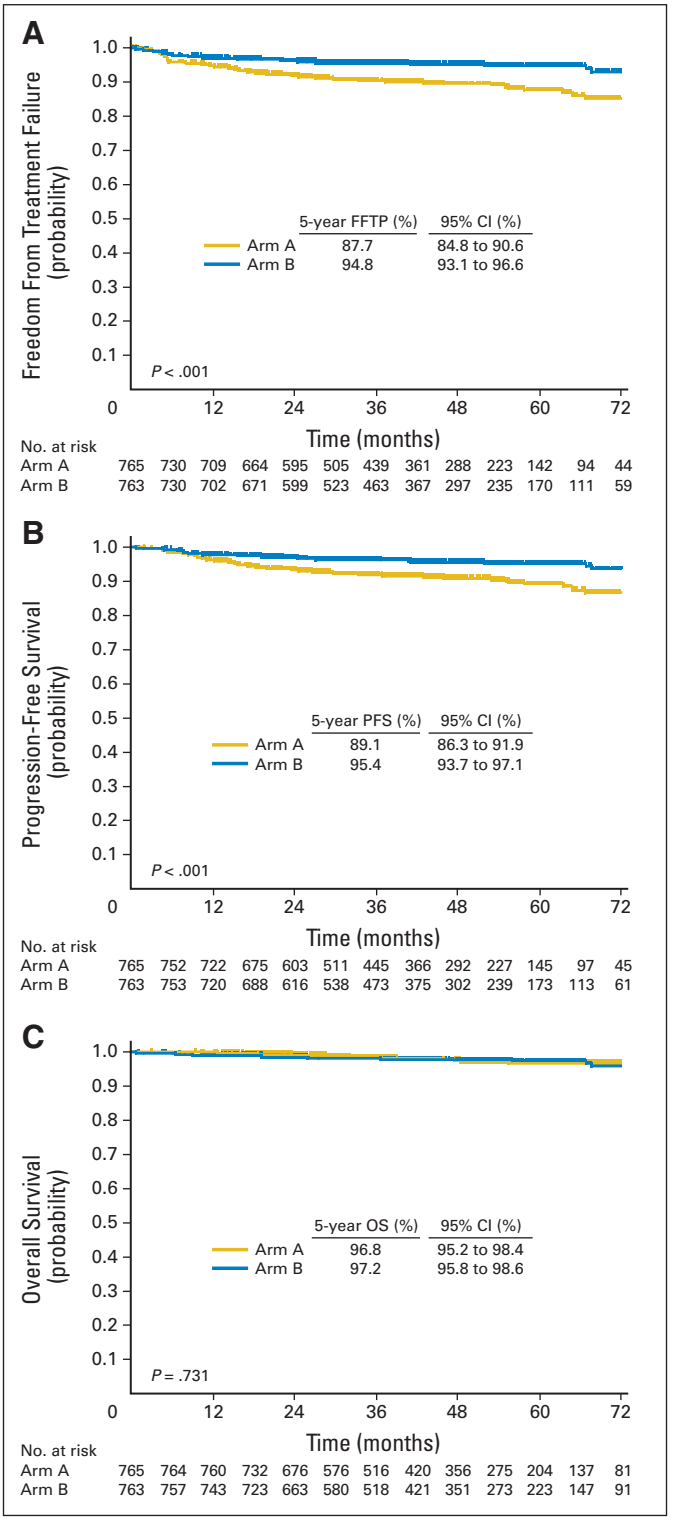

Fig 2. Kaplan-Meier curves for the primary (ie, qualified patients) analysis set of the HD14 study. (A) Freedom from treatment failure (FFTF); (B) progression-free survival (PFS); (C) overall survival (OS). Arm A received four cycles of doxorubicin, bleomycin, vinblastine, and dacarbazine (ABVD) plus 30 Gy involved-field radiotherapy (IFRT); arm B received two cycles of bleomycin, etoposide, doxorubicin, cyclophosphamide, vincristine, procarbazine, and prednisone, plus two cycles of ABVD plus 30 Gy IFRT. Median observation time was 43 months.

study[11] nor the GHSG HD11 trial[5] demonstrated better tumor control over ABVD. According to a mathematic effective dose (ED) model[12] assessing the relative potency of individual drugs in patients with HL, the ED of the newly developed 2 + 2 regimen was higher when compared with that of four cycles of ABVD (17.3 *v* 15.0) and four cycles of BEACOPP baseline (17.3 *v* 15.2).[13] In line with these calculations, HD14 demonstrates significantly better tumor control with 2 + 2 than with four cycles of ABVD in early unfavorable HL.

The improved efficacy of the 2 + 2 regimen comes at the price of more acute toxicity. There was significantly more severe (WHO grades 3 to 4) hematologic toxicity with 2 + 2 (87.1%) as compared with four cycles of ABVD (50.7%); acute treatment-related mortality in the 2 + 2 arm was 0.52%. The more pronounced acute toxicity of 2 + 2 is counterbalanced by fewer relapses and fewer patients with progressive disease. Taken together, these result in a 6.2% PFS advantage for 2 + 2 at 5 years. Because more than 50% of relapsed or progressing patients in both arms underwent successful salvage therapy, OS was not significantly different, despite the higher rate of relapse/progression in arm A.

The clinical impact of this new regimen might be challenged by putatively increased long-term toxicity of 2 + 2. However, a more detailed analysis of the current data contradicts this view. First, the

lower number of patients experiencing progression or relapse in the 2 + 2 arm (2.5% *v* 8.4%; $P < .001$) saved a significant number of patients from additional treatment including high-dose chemotherapy and the related acute and long-term toxicities.[14] Second, the higher rate of patients experiencing progression or relapse after four cycles of ABVD also resulted in a higher proportion of patients (1.4% *v* 0.4%) experiencing second relapses, for whom treatment is often palliative. Third, although a higher rate of long-term toxicity after 2 + 2 can be discussed, the total number of secondary malignancies in HD14 was similar in both arms. In addition, a recent GHSG analysis revealed no significant differences in female fertility after four cycles of ABVD or 2 + 2.[14a] Taken together, these data provide the rationale for choosing 2 + 2 as new GHSG standard for early unfavorable HL.

Large mediastinal mass and elevated ESR were adverse prognostic factors in multivariate models for FFTF and PFS in the present trial. In posthoc subgroup analyses, patients with at least one of these risk factors had pronounced PFS inferiority in arm A in comparison with those in arm B. Although the analyses were not powered to detect an interaction between treatment arm and risk group, they suggest that patients with mediastinal mass or elevated ESR particularly benefit from the intensified chemotherapy. In future trials, these risk factors might be used for more personalized treatment approaches in early unfavorable HL, together with other approaches such as positron emission tomography (PET)[15] or new biomarkers.[16]

The preceding GHSG HD11 study revealed that modestly intensified chemotherapy with BEACOPP baseline and consolidating IFRT with a reduced RT dose of 20 Gy resulted in outcomes similar to those of four cycles of ABVD followed by 30 Gy IFRT.[5] Given the higher ED of 2 + 2, it is reasonable to assume that patients might be spared the additional toxicity[17] of 30 Gy IFRT after 2 + 2 chemotherapy. Therefore, the next GHSG trial for early unfavorable HL (HD17) will compare a risk-stratified RT reduction as the experimental arm versus 2 + 2 plus 30 Gy IFRT as the standard arm. Because PET after chemotherapy has been shown to discriminate low- from high-risk HL,[18] patients in the experimental arm of HD17 with negative PET after chemotherapy will not receive RT, whereas patients with positive PET will be treated with a reduced radiation field volume applying 30 Gy involved node RT (INRT).[19,20] PET-based reduction of RT in early stage HL has already been evaluated in the EORTC/GELA (Groupe d'Etude des Lymphomes de l'Adulte)/ILL (Intergruppo Italiano Linfomi) H10 trial. Early unfavorable patients in the standard arm received four cycles of ABVD followed by 30 Gy INRT, whereas patients in the experimental arm were treated with two cycles of ABVD followed by four cycles of ABVD for patients with negative PET and two cycles of BEACOPPesc and 30 Gy INRT for patients with positive PET. However, this trial was closed early because of more events in the arms without additional RT.[21] On the basis of the superior PFS of the new 2 + 2 regimen over four cycles of ABVD, we hypothesize that 2 + 2 will be a more resilient backbone for the PET-guided omission of RT in early unfavorable HL in the HD17 trial.

In conclusion, a dose-intensification with two cycles of BEACOPPesc followed by two cycles of ABVD results in better tumor control with increased PFS as compared with standard treatment with four cycles of ABVD. The increased rate of acute toxicities in the intensified arm is overcome by fewer relapses and less second-line toxicity. The regimen of 2 + 2 plus 30 Gy IFRT is the new GHSG standard for patients with early unfavorable HL age 60 years or younger.

AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

Although all authors completed the disclosure declaration, the following author(s) indicated a financial or other interest that is relevant to the subject matter under consideration in this article. Certain relationships marked with a "U" are those for which no compensation was received; those relationships marked with a "C" were compensated. For a detailed description of the disclosure categories, or for more information about ASCO's conflict of interest policy, please refer to the Author Disclosure Declaration and the Disclosures of Potential Conflicts of Interest section in Information for Contributors.

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ORIGINAL REPORT

Short, Full-Dose Adjuvant Chemotherapy in High-Risk Adult Soft Tissue Sarcomas: A Randomized Clinical Trial From the Italian Sarcoma Group and the Spanish Sarcoma Group

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ABSTRACT

Purpose
A previous randomized clinical trial by the Italian Sarcoma Group (ISG) had shown a survival benefit of adjuvant chemotherapy (CT) in high-risk extremity soft tissue sarcoma (STS). However, the dose-intensity of the last two cycles was suboptimal. We then undertook a multicentric international phase III study to compare three and five cycles of the same CT.

Patients and Methods
Patients were randomly assigned either to receive three cycles of preoperative CT with epirubicin 120 mg/m^2 and ifosfamide 9 g/m^2 and granulocyte colony-stimulating factor (arm A) or to receive the same three cycles of preoperative CT followed by two further cycles of postoperative CT (arm B). Noninferiority of the primary end point, overall survival (OS), was assessed by the CI of the hazard ratio (HR; arm A/arm B) obtained from the Cox model.

Results
Between January 2002 and April 2007, 328 patients were recruited (164 patients in each arm). At a median follow-up of 63 months (interquartile range, 49 to 77 months), 100 deaths were recorded, 49 in arm A and 51 in arm B. Five-year OS probability was 0.70 for the entire group of patients (0.68 in arm A and 0.71 in arm B). The HR of arm A versus arm B was 1.00 (90% CI, 0.72 to 1.39).

Conclusion
In this population of patients with high-risk localized STS, three cycles of full-dose preoperative CT were not inferior to five cycles. The outcome compares favorably with the expected survival of patients with high-risk STS and was superimposable on the CT arm of the previous ISG trial.

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INTRODUCTION

Standard treatment of localized high-risk soft tissue sarcoma (STS) of the extremities and trunk wall consists of surgery and radiation therapy (RT).[1,2] RT can be delivered either postoperatively[3,4] or preoperatively.[5] Adjuvant chemotherapy (CT) is not standard treatment, but clinical practice guidelines encompass it as an option in high-risk patients.[1,2] This is a result of the heterogeneous outcome of several clinical trials. A meta-analysis showed a statistically significant, albeit limited, benefit for adjuvant CT,[6] but a preliminarily reported large clinical trial of the European Organisation for Research and Treatment of Cancer Soft Tissue and Bone Sarcoma Group was not included.[7] However, the previous trial of the Italian Sarcoma Group (ISG) was closed in advance because of the early observation of a substantial survival benefit in favor of the CT arm.[8] This trial was marked by the selection of a high-risk patient population and the use of a full-dose anthracycline plus ifosfamide regimen. The limited number of enrolled patients was the main cause for the loss of statistical significance on a longer follow-up.[9]

An observation of the previous ISG trial was that the dose-intensity of the last two cycles of CT had dropped. A hypothesis could then be that the first three cycles were the most significant to the final outcome.

Therefore, we decided to select the same high-risk patient population of the previous ISG trial. We used the same full-dose regimen combining an anthracycline with ifosfamide. We administered three cycles of CT preoperatively and then compared an experimental arm in which no further CT was given against a conventional arm in which patients received a further two cycles of CT postoperatively (for a total of five cycles, as in the previous ISG trial).

PATIENTS AND METHODS

Patients

Patients were recruited from 10 sites in Italy and nine sites in Spain. Eligibility criteria included age ≥ 18 years and histologically proven localized adult-type STS located to the extremities or trunk wall that was deeply seated (according to the investing fascia), with largest diameter of ≥ 5 cm if primary or any size if locally recurrent and with histologic grade of aggressiveness equal to 3 according to the Fédération Nationale des Centres de Lutte Contre le Cancer.[10] Alveolar soft part sarcoma, epithelioid sarcoma, clear cell sarcoma, and pediatric-type sarcoma were excluded. Other inclusion criteria included Eastern Cooperative Oncology Group performance status ≤ 1 and adequate bone marrow (WBC > 3,500/μL, neutrophils > 1,500/μL, platelets > 150,000/μL, and hemoglobin > 11 g/dL), renal (serum creatinine < 1.3 mg/dL), hepatic (total bilirubin ≤ 1.5 mg/dL and ALT and AST < 2× normal value), and cardiac (left cardiac ejection fraction ≥ 50%) function. The study protocol was approved by institutional review boards according to applicable laws in the two participating countries. Written informed consent was obtained from all patients. The study was registered at the Italian Trial Observatory (European Union Drug Regulating Authorities Clinical Trials No. 2004-003979-36). The study was conducted in accordance with the Declaration of Helsinki and the Good Clinical Practice guidelines.

Procedures

Patients were randomly assigned at the Controlled Clinical Trial Office of Istituto Nazionale Tumori (Milan, Italy) to receive either three preoperative cycles (arm A) or three preoperative and two postoperative cycles (arm B) of epirubicin and ifosfamide at full doses. CT had to be repeated every 21 days and included epirubicin 60 mg/m^2/d, short infusion, on days 1 and 2 plus ifosfamide 3 g/m^2/d on days 1, 2, and 3. Mesna 1,000 mg/m^2 (every 3 to 4 hours for 3 days) was also administered on days 1, 2, and 3. In the interval period, granulocyte colony-stimulating factor (G-CSF; any formulation) was administered at a dose of 300 μg subcutaneously from day 7 to day 14 or until WBC count recovered completely (two successive WBC counts > 5,000/μL or one WBC count > 10,000/μL) or in any case until postnadir (day 10 to 12). If neutrophils failed to recover to normal values (> 1,500/μL), treatment with G-CSF was continued until these values were reached. CT was never resumed before 48 hours after the end of G-CSF administration.

We graded toxic effects according to the National Cancer Institute Common Toxicity Criteria, version 2.0. Dose reductions for toxicities are listed in Appendix Table A1 (online only).

RT could be either given preoperatively or postoperatively at the discretion of the treating physician, concurrent to the administration of CT. A total dose of 44 to 50.4 Gy was foreseen in the preoperative setting, whereas the dose was 60 to 66 Gy in the postoperative setting. Patients treated with preoperative RT could also receive an intraoperative (10 to 12 Gy) or postoperative boost (16 to 20 Gy) at the discretion of the treating physician. At the time of surgery, response was assessed by RECIST.[11]

Surgery was planned 3 to 4 weeks after the administration of the last preoperative cycle and not before 4 weeks after the end of preoperative RT. Postoperative CT was planned 3 weeks after surgery. Postoperative RT was usually started within 6 weeks after surgery and could be given concurrent to postoperative CT in the arm receiving five cycles of CT.

Follow-up was performed every 3 months for the first 3 years after the end of treatment by contrast-enhanced chest computed tomography and magnetic resonance imaging or computed tomography of the affected site. Follow-up was performed every 6 months during years 4 and 5 after the end of treatment and then yearly thereafter.

Statistical Analysis

The study was designed to show noninferiority of three cycles (arm A) versus five cycles (arm B) of CT with respect to the primary end point of overall survival (OS), defined both as the interval between random assignment and death and between surgery and death. A sample size of 150 patients per arm was planned. As prespecified in the protocol, three cycles of CT were considered not inferior to five cycles if the upper limit of the 90% CI of the hazard ratio (HR) estimated by the Cox regression model[12] was less than 1.5.[13] By recruiting 164 patients for each arm, a study power of greater than 80% was achieved by assuming an expected 5-year survival of 45% in patients treated with five cycles (control group) and of approximately 70% when the assumed 5-year survival in the control group moved from 45% to 60%. The survival pattern was estimated by means of the Kaplan-Meier method.[14] When the risk of local and distant relapses after surgery was assessed, data were processed according to the competing risks approach.[15] The primary study outcome was evaluated according to the intent-to-treat (ITT) principle by including all patients who underwent random assignment and signed the informed consent form. A per-protocol analysis was also carried out, in which 240 patients (134 patients in arm A and 106 patients in arm B) without any major protocol deviations were included. All other results are presented only for the ITT sample. In an additional analysis, we also investigated the prognostic role on OS of conventional variables (age, phase at study entry [primary or locally recurrent], histologic subtype, microscopic margins status, and tumor size) and of treatment arm using a Cox regression model in both univariable and multivariable fashion. In this model, each regression coefficient represents the logarithm of the HR, which is assumed to be constant over time. Under the null hypothesis that a variable has no prognostic role, HR is expected to be 1.00. The hypothesis of HR = 1.00 was tested using the Wald statistic. Age and tumor size were analyzed as continuous variables. The relationship between them and the outcome was investigated by resorting to a regression model based on restricted cubic splines.[16] All statistical analyses were performed with the SAS software (version 9.2; SAS Institute, Cary, NC).

RESULTS

Patient Population

Three hundred twenty-eight patients were randomly assigned from January 2002 to March 2007 (Fig 1). Two hundred twenty-two patients were available for central pathologic review. The ITT sample comprised all randomly assigned patients, although seven patients were retrospectively found to be ineligible for major violations (four major histologic inconsistencies and three consent withdrawals). Patient demographics and clinical characteristics, overall and per treatment arm, are listed in Table 1.

Toxicity

Hematologic and nonhematologic toxicities were consistent with the ones already reported for this regimen. Detailed data are provided in Table 2. The first three cycles were completed by 289 patients (139 patients in arm A and 150 patients in arm B). Among the 139 patients in arm A who completed the first three cycles, three patients experienced distant progression before surgery, and two additional patients were retrospectively found to be ineligible as a result of major histologic inconsistencies. Among the 150 patients in arm B who completed the first three cycles, only 106 patients also completed the two postoperative cycles.

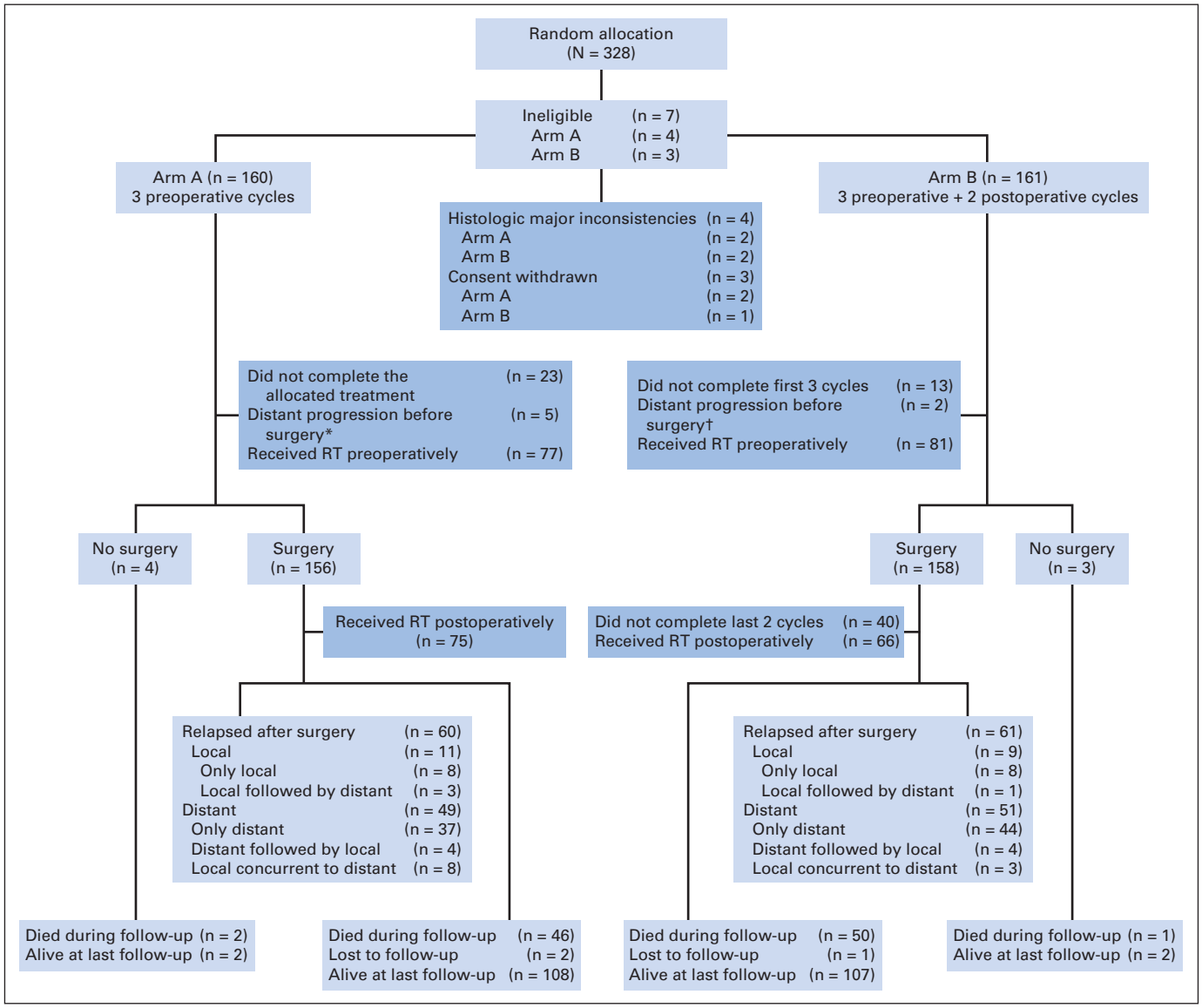

Fig 1. CONSORT diagram. RT, radiation therapy. (*) Two patients with distant progression before surgery did not complete the allocated treatment (arm A). (†) One patient with distant progression before surgery did not complete the first three cycles (arm B).

The main reason for not completing the postoperative therapy in arm B was patient refusal. Dose-intensity for patients completing the number of cycles of the allocated treatment is provided in Appendix Tables A2, A3, and A4 (online only).[17]

Primary End Points

Median follow-up of the ITT population was 63 months (interquartile range, 49 to 77 months) from random assignment and 60 months (interquartile range, 47 to 74 months) from surgery. One hundred patients died after random assignment (49 patients in arm A and 51 patients in arm B), and 96 patients died after surgery (46 patients in arm A and 50 patients in arm B).

By considering the ITT series, the probability of OS from random assignment was 0.70 (95% CI, 0.64 to 0.74) at 5 years; the probabilities were 0.68 (95% CI, 0.60 to 0.75) in arm A and 0.71 (95% CI, 0.63 to 0.77) in arm B (Fig 2A). The HR of arm A versus arm B was 1.00 (90% CI, 0.72 to 1.39). Similar figures were obtained for OS from surgery, which was 0.70 (95% CI, 0.64 to 0.75) overall, 0.69 (95% CI, 0.60 to 0.76) in arm A, and 0.71 (95% CI, 0.63 to 0.77) in arm B (Fig 2B) at 5 years. The HR of arm A versus arm B was 0.96 (90% CI, 0.69 to 1.34). A per-protocol analysis confirmed these results (HR, 0.99; 90% CI, 0.66 to 1.48; Appendix Figs A1A and A1B, online only). Thus, three and five cycles of CT showed an equivalent efficacy by considering the prespecified noninferiority margin of 1.50 of the upper limit of the 90% CI of the HR.

Seven patients experienced distant progression before surgery during the preoperative treatment (five patients in arm A and two patients in arm B). Twenty patients (11 in arm A and nine in arm B) developed local recurrence after surgery as the primary event; 11 patients (eight in arm A and three in arm B) developed local recurrence concurrent with distant metastases, and nine patients (four in arm A and five in arm B) developed local recurrence after distant metastases. One hundred two patients (50 in arm A and 52 in arm B)

Table 1. Patient Demographics and Clinical Characteristics

Demographic or Clinical Characteristic	Arm A		Arm B		Total	
	No. of Patients	%	No. of Patients	%	No. of Patients	%
Patients enrolled	164	50	164	50	328	100
Phase						
Locally recurrent	7	2.13	6	1.83	13	3.96
Primary	154	46.95	156	47.56	310	94.51
Missing	3	0.91	2	0.61	5	1.52
Re-excision (previous inadequate resection at study entry)						
Yes	32	9.76	23	7.01	55	16.77
No	129	39.33	139	42.33	268	81.66
Missing	3	0.91	2	0.61	5	1.52
Histologic subtype						
Undifferentiated pleomorphic sarcoma	69	21.04	57	17.38	126	38.42
Leiomyosarcoma	20	6.10	23	7.01	43	13.11
Synovial sarcoma	32	9.76	39	11.89	71	21.65
Other	43	13.11	45	13.72	88	26.83
Site of origin						
Upper extremity	16	4.88	22	6.71	38	11.59
Lower extremity	102	31.10	100	30.49	202	61.59
Scapular girdle	16	4.88	13	3.96	29	8.84
Pelvic girdle	14	4.27	20	6.10	34	10.37
Chest wall	5	1.52	2	0.61	7	2.13
Abdominal wall	5	1.52	—	—	5	1.52
Paravertebral	4	1.22	5	1.52	9	2.74
Missing	2	0.61	2	0.61	4	1.22
Microscopic margin status						
Positive	17	5.18	12	3.66	29	8.84
Negative	134	40.85	144	43.90	278	84.75
Missing	13	3.96	8	2.44	21	6.40
Type of surgery according to site						
Extremity + girdle	148	45.12	155	47.26	303	92.38
Amputation	11	3.35	15	4.57	26	7.92
Conservative	131	39.94	137	41.77	268	81.71
No surgery	6	1.83	3	0.91	9	2.74
Trunk wall	14	4.27	7	2.13	21	6.40
Conservative	14	4.27	7	2.13	21	6.40
Missing	2	0.61	2	0.61	4	1.22
Conservative	2	0.61	1	0.30	3	0.91
No surgery	—	—	1	0.30	1	0.30
Preoperative RT						
Yes	78	23.78	82	25.00	160	48.78
No	86	26.22	82	25.00	168	51.22
Postoperative RT						
Yes	75	22.87	66	20.12	141	42.99
No	87	26.52	94	28.66	181	55.18
Missing	2	0.61	4	1.22	6	1.83
Age, years						
Median	51		47		48.5	
Range	15-79		16-74		15-79	
Tumor size, cm						
Median	10		10		10	
Range	2-45		3-30		2-45	

Abbreviation: RT, radiation therapy.

Table 2. Hematologic and Nonhematologic Toxicity During the Three Cycles of Preoperative Chemotherapy (arms A and B) and During the Two Cycles of Postoperative Chemotherapy (arm B)

Toxicity	Preoperative Chemotherapy		Postoperative Chemotherapy (arm B)‡
	Arm A*	Arm B†	
Hematologic toxicity			
WBC			
Nadir value, /μL	379	403	183
Grade 3, %	26	26	23
Grade 4, %	49	49	62
Absolute neutrophil count			
Nadir value, /μL	345	363	165
Grade 3, %	17	14	13
Grade 4, %	60	61	70
Platelets			
Nadir value, /μL	380	401	183
Grade 3, %	14	16	20
Grade 4, %	2	2	2
Nonhematologic toxicity, % of patients			
Cardiac	1.3	—	—
Constitutional symptoms	1.9	1.9	—
Febrile neutropenia	11.4	7.4	6.1
Fever	—	0.6	—
GI	13.3	14.9	4.6
Infection	0.6	0.6	—
Neurologic	1.9	—	—
Pain	0.6	—	—
Pulmonary	0.6	—	—
Renal failure	—	—	1.5

*Patients who at least started first cycle (n = 158).
†Patients who at least started first cycle (n = 161).
‡Patients who at least started first cycle (n = 130).

experienced distant metastases as the primary event after surgery either alone (n = 82) or concurrent with local recurrence (n = 20), whereas four patients (three in arm A and one in arm B) developed distant metastases after local recurrence.

Overall 5-year cumulative incidence of local recurrence was 0.062 (SE, 0.014), 0.065 (SE, 0.020) in arm A, and 0.059 (SE, 0.019) in arm B (Fig 3). The overall 5-year cumulative incidence of distant metastases was 0.326 (SE, 0.027), 0.321 (SE, 0.039) in arm A, and 0.033 (SE, 0.038) in arm B (Fig 3).

Response Rate

A central radiologic response assessment was performed for all patients. Fifty-five patients could not be evaluated (37 for having started the treatment with no measurable disease 18 for missing baseline cross-sectional images).

As for the remaining 273 patients, according to RECIST at the time of surgery, no complete responses were observed. Sixty-six patients (36 in arm A and 30 in arm B) obtained a partial response. One hundred sixty-nine patients (77 in arm A and 92 in arm B) had stable disease, and 38 patients (20 in arm A and 18 in arm B) had progressive disease. Forty-six additional patients among those who qualified as having stable disease according to RECIST had a minor dimensional response, defined as a $\geq$ 10% but less than 30% decrease in largest tumor diameter.

Additional Analyses

By considering OS for both of the continuous variables (age and tumor size) used in the Cox regression models, a linear relationship

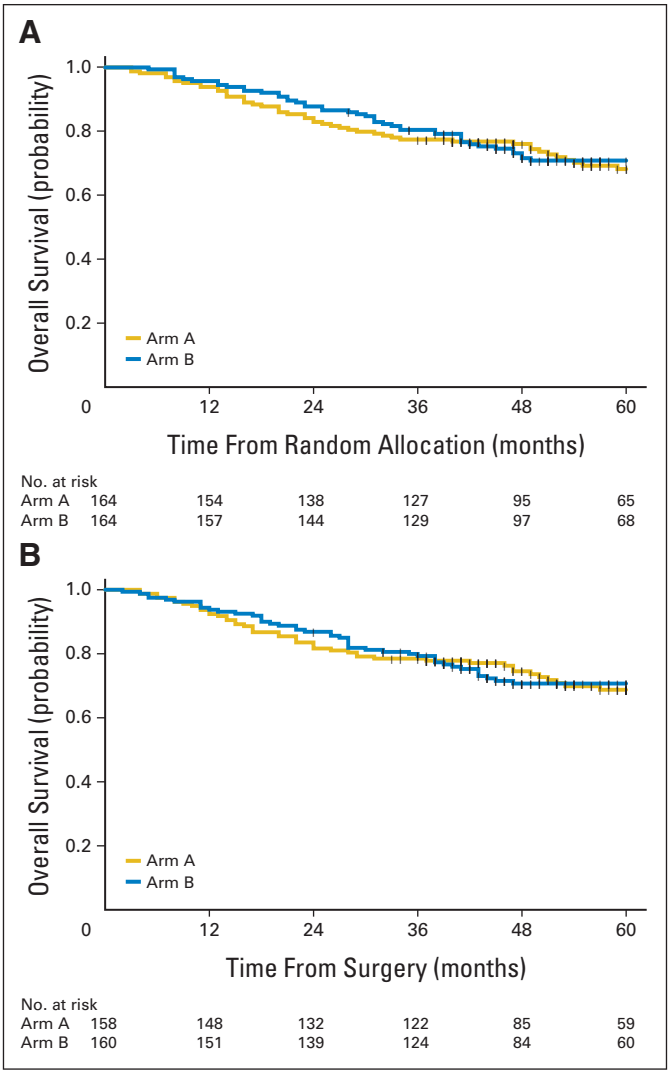

Fig 2. Five-year probability of overall survival (A) from random assignment and (B) from surgery according to study arm.

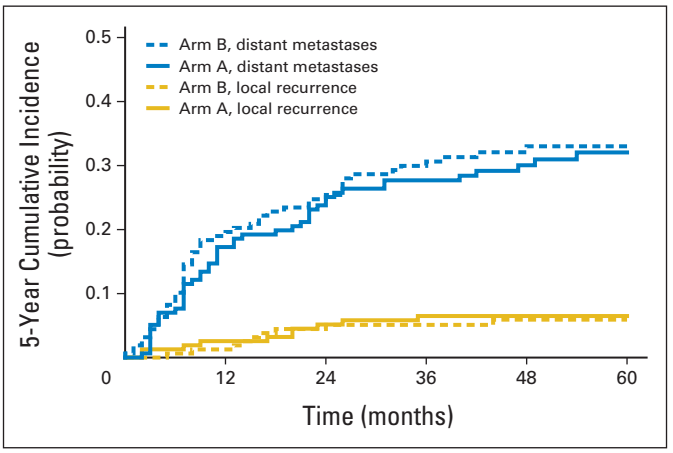

Fig 3. Five-year cumulative incidence of local recurrence and distant metastases according to study arm.

between the logarithm of hazard and their values was found to be appropriate. Univariable and multivariable analyses showed that histologic subtype and tumor size were significantly associated with OS (Appendix Table A5, online only, and Table 3).

In the whole series, the 5-year survival predicted in our series by the Memorial Sloan-Kettering Cancer Center nomogram[17] was 62.7% (95% CI, 54.1% to 71.0%); the observed survival was 69.7% (95% CI, 64.6% to 75.3%). When restricted to the extremities subset, the 5-year survival predicted by the Milan nomogram[18] was 56.6% (95% CI, 49.6% to 63.4%) versus the observed survival of 68.6% (95% CI, 63.2% to 74.5%). These two comparisons are shown in Figures 4A and 4B.

DISCUSSION

In this randomized clinical trial, 328 patients with localized high-risk STS of the extremities and trunk wall had 5-year OS and recurrence-free survival rates averaging 70% and 60%, respectively, with no difference regarding whether patients received three or five cycles of full-dose CT with anthracyclines plus ifosfamide (Fig 2). The ITT analysis shows that three cycles of full-dose CT were not inferior to five cycles. Per-protocol analysis confirmed these results. Three cycles were given preoperatively in all patients, with concomitant RT given in half. The outcome was comparable to that of the CT arm of the previous ISG trial, which was carried out in a similar patient population using the same chemotherapeutic regimen. The outcome compared favorably with predictions from both the Memorial Sloan-Kettering Cancer Center[18] and Milan prognostic nomograms,[19] although these nomograms are based on nontrial series (Figs 4A and 4B).

Adjuvant, or neoadjuvant, CT is not viewed as a standard therapy in current treatment of localized STS. However, an updated meta-analysis[6] of randomized trials showed a statistically significant advantage in terms of both recurrence-free survival and OS. In addition to excluding a major, negative, unpublished trial, this meta-analysis was not based on individual data. However, it included all published randomized trials, many of which were biased against CT inasmuch as they used doxorubicin-based regimens, without ifosfamide. The benefit was limited but similar to the benefit suggested by the comparison we made between our results and predictions from the currently available prognostic nomograms (Figs 4A and 4B).

In the end, current clinical practice guidelines[1,2] foresee CT as an option when the patient risk is substantial, as in our population. This

Table 3. Multivariable Cox Regression Analysis on Overall Survival: Final Model

Variables	HR	95% CI	Wald *P**
Histologic subtype			
Leiomyosarcoma *v* MFH/UPS + spindle cell sarcoma NOS	3.17	1.80 to 5.59	< .01
Synovial sarcoma *v* MFH/UPS + spindle cell sarcoma NOS	2.05	1.16 to 3.63	.01
Other *v* MFH/UPS + spindle cell sarcoma NOS	1.39	0.79 to 2.43	.25
Tumor size (continuous)	1.06	1.02 to 1.10	< .01

Abbreviations: HR, hazard ratio; MFH, malignant fibrous histiocytoma; NOS, not otherwise specified; UPS, undifferentiated pleomorphic sarcoma.
**P* value associated with the Wald statistic.

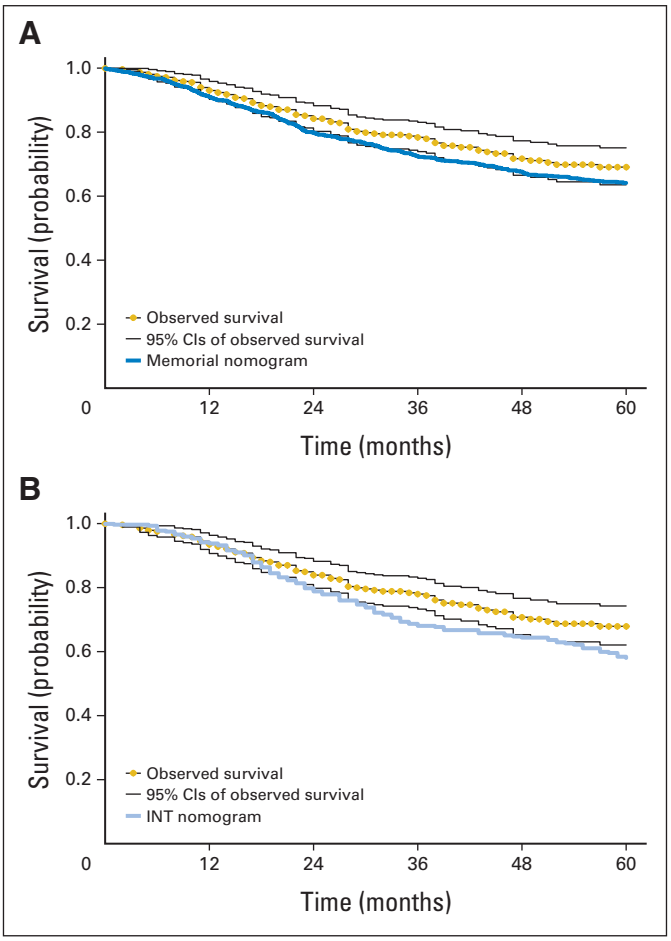

Fig 4. Observed Kaplan-Meier survival curves versus survival curves predicted by (A) the Memorial Sloan-Kettering Cancer Center nomogram and (B) the Milan nomogram. Predicted curves were constructed as the average of the survival curves predicted at the individual level; curves in (B) were obtained in the patient subset with extremity soft tissue sarcoma. INT, Istituto Nazionale Tumori.

trial shows that three courses of full-dose CT may be a choice when the decision is to resort to CT in high-risk patients with STS.

A major limitation of this trial is the limited power. Indeed, this is the third randomized clinical trial ever, to our knowledge, on adjuvant CT for STS. However, because it was planned as a noninferiority trial, the trial was powered to detect a clinically acceptable difference, the level of which was defined by an upper limit of the 90% CI of less than 1.5. As a matter of fact, the trial resulted in two curves that are superimposable. However, the upper 90% CI of their difference is 1.39. We believe that within a shared decision-making setting, like the one that occurs with patients with STS amenable to adjuvant therapy, this uncertainty can be accommodated together with all other uncertainties regarding the value of adjuvant CT.

The rationale for decreasing the number of cycles of CT to three was that in the previous ISG trial a decrease in dose-intensity was seen for the last two cycles. This was not observed in the current trial; in the current trial, the last two cycles followed surgery, so that they were distanced from the first three cycles. This is also a theoretical limitation of our conclusion in regard to the optimal number of cycles. In fact, we compared five cycles, split preoperatively and postoperatively, with three cycles preoperatively. In other words, the comparison was not made between three and five consecutive cycles. However, one should be aware of the potential decrease in dose-intensity when consecutive cycles are administered. In addition, as mentioned earlier, our results were comparable to the previous ISG trial, which used five consecutive courses.

We decided to place the adjuvant treatment preoperatively. We are aware that neoadjuvant CT likely has little extra value in solid tumors if one considers the final outcome. When neoadjuvant CT was formally compared with postoperative CT in the solid tumor where it is used more classically, osteosarcoma, no difference could be found.[20] However, high-risk STSs are often challenging regarding local treatment. Conservative, function-preserving, wide resection is the goal, and the quality of local control needs to be viewed against the quality of subsequent life. In this trial, the objective response rate was 25%, but minor responses were observed in up to 41% of patients. Minor variations in tumor size and tumor characteristics may be meaningful for surgery. In addition, preoperative RT was administered in one half of patients, without major adverse effects. Interestingly, the dose-intensity of CT was maintained as well. The number of primary amputations ($<$ 10% of patients with extremity tumors) and the good local control in this selected high-risk patient population are worth noticing. Interestingly, we found that the status of microscopic margins was not a prognostic marker for survival, as observed in other series.[21] Our conclusion is that, when an adjuvant CT is considered in relation to the systemic risk factors, it may well be administered in the preoperative phase, possibly contributing to local control and residual limb function.

On multivariable analysis, histologic subtype was significantly associated with differences in outcome. In particular, leiomyosarcoma fared worse. Current medical therapy of advanced STS is marked by a reappraisal of histology, at a time when targeted therapies are intensively studied. However, even cytotoxic CT seems to exert a different antitumor activity depending on the histology, as is the case with gemcitabine for leiomyosarcoma,[22] trabectedin for liposarcoma and leiomyosarcoma,[23] and gemcitabine and taxanes for angiosarcoma.[24] An assessment of the antitumor activity of preoperative CT according to the histologic type is ongoing. Our next clinical trial will assess whether tailoring the three preoperative courses of CT to the histologic STS subtype may provide an advantage compared with using epirubicin plus ifosfamide in all patients.

In conclusion, when adjuvant CT is selected for a patient with high-risk STS, three cycles of anthracyclines plus ifosfamide may be considered. Toxicity is limited. CT can be administered preoperatively and also combined with RT, depending on the surgical needs. The value of a histology-driven selection for preoperative CT is the subject of an ongoing clinical trial.

AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

The author(s) indicated no potential conflicts of interest.

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ORIGINAL REPORT

Advanced Stage, Increased Lactate Dehydrogenase, and Primary Site, but Not Adolescent Age (≥ 15 Years), Are Associated With an Increased Risk of Treatment Failure in Children and Adolescents With Mature B-Cell Non-Hodgkin's Lymphoma: Results of the FAB LMB 96 Study

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Authors' disclosures of potential conflicts of interest and author contributions are found at the end of this article.

Clinical Trials repository link available on JCO.org.

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ABSTRACT

Purpose
Adolescents (age 15 to 21 years) compared with younger children with mature B-cell non-Hodgkin's lymphoma (NHL) have been historically considered to have an inferior prognosis. We therefore analyzed the impact of age and other diagnostic factors on the risk of treatment failure in children and adolescents treated on the French-American-British Mature B-Cell Lymphoma 96 (FAB LMB 96) trial.

Patients and Methods
Patients were divided by risk: group A (limited), group B (intermediate), and group C (advanced), as previously described. Prognostic factors analyzed for event-free survival (EFS) included age (< 15 *v* ≥ 15 years), stage (I/II *v* III/IV), primary site, lactate dehydrogenase (LDH), bone marrow/CNS (BM/CNS) involvement, and histology (diffuse large B-cell lymphoma *v* mediastinal B-cell lymphoma *v* Burkitt lymphoma or Burkitt-like lymphoma).

Results
The 3-year EFS for the whole cohort was 88% ± 1%. Age was not associated as a risk factor for increased treatment failure in either univariate analysis ($P = .15$) or multivariate analysis ($P = .58$). Increased LDH (≥ 2 × upper limit of normal [ULN] *v* < 2 × ULN), primary site, and BM-positive/CNS-positive disease were all independent risk factors associated with a significant increase in treatment failure rate (relative risk, 2.0; $P < .001$, $P < .012$, and $P < .001$, respectively).

Conclusion
LDH level at diagnosis, mediastinal disease, and combined BM-positive/CNS-positive involvement are independent risk factors in children with mature B-cell NHL. Future studies should be developed to identify specific therapeutic strategies (immunotherapy) to overcome these risk factors and to identify the biologic basis associated with these prognostic factors in children with mature B-cell NHL.

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INTRODUCTION

Mature B-cell non-Hodgkin's lymphoma (NHL), including Burkitt lymphoma (BL), Burkitt leukemia, diffuse large B-cell lymphoma (DLBCL), and primary mediastinal B-cell lymphoma (PMBL) make up approximately 60% of all malignant NHLs that occur in children and adolescents.[1,2] Multidisciplinary pediatric cooperative group collaborations over the past 25 years have reported a 99% survival rate in limited-risk patients, a 90% survival rate in intermediate-risk patients, and an approximate 70% to 80% overall survival (OS) rate in children with advanced-risk mature B-cell NHL.[3-16]

Several risk factors have been associated with influencing event-free survival (EFS) in children with mature B-cell NHL. Advanced stage (Murphy classification; ie, stages III and IV *v* stages I and II) has been associated with a decrease in EFS in children and adolescents with mature B-cell NHL.[12-14,16] Increased lactate dehydrogenase (LDH) at diagnosis, either ≥ 2 × upper limit of normal (ULN) or ≥ 1,000 IU has also been associated with a significant decrease in EFS in children and

adolescents with mature B-cell NHL.[6,12-14,16] CNS involvement has also been an independent poor-risk factor on EFS in children with mature B-cell NHL.[6,12-14,16] Response to reduction therapy following a reductive phase of chemotherapy in children and adolescents with mature B-cell NHL has also been associated with a significantly inferior EFS, particularly in patients with intermediate and advanced risk.[6,12,13]

Age, particularly those in the adolescent age group (15 to 21 years), has been suggested to be an additional potential independent prognostic risk factor in EFS in children and adolescents with mature B-cell NHL. Malignant lymphomas are the most common malignancy in the adolescent age group, representing approximately 26% of all malignancies.[17] The first NHL treatment protocol—CCG-551—in the Children's Cancer Group (CCG) from 1977 to 1982 demonstrated that adolescents versus children younger than 15 years of age with BL treated with either cyclophosphamide, vincristine, methotrexate, and prednisone (COMP) or with LSA_2 L_2 therapy (cyclophosphamide, vincristine, methotrexate, daunomycin, prednisone, cytarabine, thioguanine, asparaginase, methotrexate, and carmustine) had a significantly inferior EFS (25% *v* 70%; $P < .033$).[18-20] Subsequently, the CCG performed a retrospective review of all consecutive CCG studies between 1977 and 1994 that treated children and adolescents with BL or Burkitt-like lymphoma (BLL) and demonstrated a significant decrease in 5-year EFS in adolescents versus younger children treated on similar therapy.[9] Similarly, Patte et al[13] reported that the LMB 89 mature B-cell lymphoma protocol results demonstrated a significantly increased risk of relapse in patients 15 years of age or older. We previously reported the primary results of the French-American-British Mature B-Cell Lymphoma 96 (FAB LMB 96) study.[6,10,12] In this report, we investigated the prognostic risk of adolescent age (15 to 21 years) and other prognostic factors on 5-year EFS and OS in a combined cohort of 1,111 patients with mature B-cell NHL registered and treated on this uniform international cooperative group protocol, which used modern, short, and intensive multiagent chemotherapy.

PATIENTS AND METHODS

FAB LMB 96 was an international study from 161 treatment centers by three cooperative groups: Children's Oncology Group (COG; former CCG institutions in the United States, Canada, and Australia), the United Kingdom Children's Cancer Study Group (UKCCSG), and Societe Francaise d'Oncologie Pediatrique (SFOP; institutions in France and some centers in Belgium and the Netherlands). The protocol was approved by all of the local institutional review boards, and written informed consent was obtained in accordance with the Declaration of Helsinki. The study opened in May 1996 and closed to patient accrual in June 2001.

Eligibility

Children and adolescents with newly diagnosed mature B-lineage NHL with BL, DLBCL, or BLL, according to the Revised European-American Lymphoma (REAL) classification, were eligible.[21] Staging was performed as previously described by Murphy et al.[22] Risk classification was defined as low risk (group A) with resected stage I and abdominal completely resected stage II, high risk (group C) with bone marrow (BM) involvement (L3 blasts $\geq$ 25% and/or CNS disease), and intermediate risk (group B) was all others.[6,10,12] Exclusion criteria included congenital or acquired immunodeficiency, prior malignancy, or prior chemotherapy. Therapy for group A involved a nonrandomized confirmatory study of brief chemotherapy[10]; therapy for groups B and C involved an open randomized trial that investigated the reduction of treatment.[6,12]

Treatment

Group A. Patients assigned to group A following resection and diagnostic workup received two courses of cyclophosphamide, vincristine, prednisone, and doxorubicin (COPAD) without intrathecal (IT) chemotherapy, as we have previously described (Fig 1A).[10]

Group B. The details of treatment and random assignment have been described previously.[12] Patients received 7-day, low-dose, prophase cyclophosphamide, vincristine, and prednisone (COP) therapy. Induction therapy consisted of two cycles of fractionated COPAD and high-dose methotrexate 3 g/m^2 (HD-MTX; COPADM). Patients then received two consolidation cycles of cytarabine and HD-MTX (CYM). Treatment concluded with one maintenance phase of COPADM (COPADM-3). Patients received IT chemotherapy prophylaxis during all phases of the therapy. As previously described, patients who did not progress during the first induction course were randomly assigned to therapy reduction with 50% cyclophosphamide delivered in the second induction cycle and/or the elimination of maintenance therapy in a four-arm stratified random assignment. Patients with less than a 20% response on day 7 of COP and patients with residual disease after CYM-1 (that is, the first cycle of CYM) were transferred to rescue group C therapy as outlined below in Figure 1B.[6,12]

Group C. The details of treatment and random assignment are as previously reported.[6] Patients received 7-day low-dose prophase COP. Induction therapy consisted of two cycles of COPADM (with HD-MTX 8 g/m^2). Consolidation consisted of high-dose and continuous cytarabine with etoposide (CYVE). Patients with CNS disease did not receive cranial radiation but received additional IT therapy as well as an additional HD-MTX course between consolidation courses (Figs 1C and 1D, respectively). The first maintenance cycle consisted of COPADM, and three additional maintenance cycles followed in the standard arm of therapy. Patients with favorable disease reassessments were randomly assigned to reduction in chemotherapy during the consolidation phase (CYVE) and the elimination of the three maintenance arms in a two-arm random assignment.[6]

Definition, Eligibility, and Random Assignment of Adolescents

The upper age limit of enrollment was 21 years at diagnosis in COG institutions and 18 years at diagnosis in SFOP and UKCCSG institutions. The definition of adolescence for subsequent analysis included patients age $\geq$ 15 years at study enrollment. In the randomized analysis, patients were randomly assigned within cooperative groups and strata defined by all combinations of cooperative group, histology (DLBCL or not), stage and LDH level (group B), and CNS positivity (group C). No a priori stratification occurred on the basis of age at enrollment. The distribution of adolescents in the randomized arms was not planned or stratified in advance.

Hematopathology

The morphology and immunophenotype from the initial diagnostic material from each patient was independently evaluated by each of the six hematopathologists from the three national cooperative groups (SFOP: M. Raphael, M.J. Terrier-Lacombe; CCG: M.A. Lones, S.L. Perkins; UKCCSG: K. McCarthy, K.A. Wotherspoon) to establish a diagnosis. The initial standard immunophenotyping panel included antibodies to the following CD antigens: CD20, CD79a, CD3, CD45RO, TDT, CD30, and p80, as described previously.[23,24] The protocol cases were classified according to the criteria described in the REAL and WHO classifications.[23,24] At initial evaluation, only clinical information on biopsy site, age, and sex were known. All mediastinal cases were reviewed again by the pathology group at a multiheaded microscope, with full knowledge of all available clinical and cytogenetic information and with careful attention to morphologic features of sclerosis, clear-cell change, and immunophenotype. Because of the limited amount of tissue available, design of the protocol, and the availability of antibodies at the time of review, additional immunohistochemical staining could not be performed, Results of morphologic and immunophenotypic evaluations, as well as diagnosis, were recorded on a standard form for entry into a computer database. A national consensus diagnosis was established for each patient on the basis of independent agreement by the group of hematopathologists or following review by the national group on a multiheaded microscope. A final consensus diagnosis was established for each patient when at least two of the three national consensus

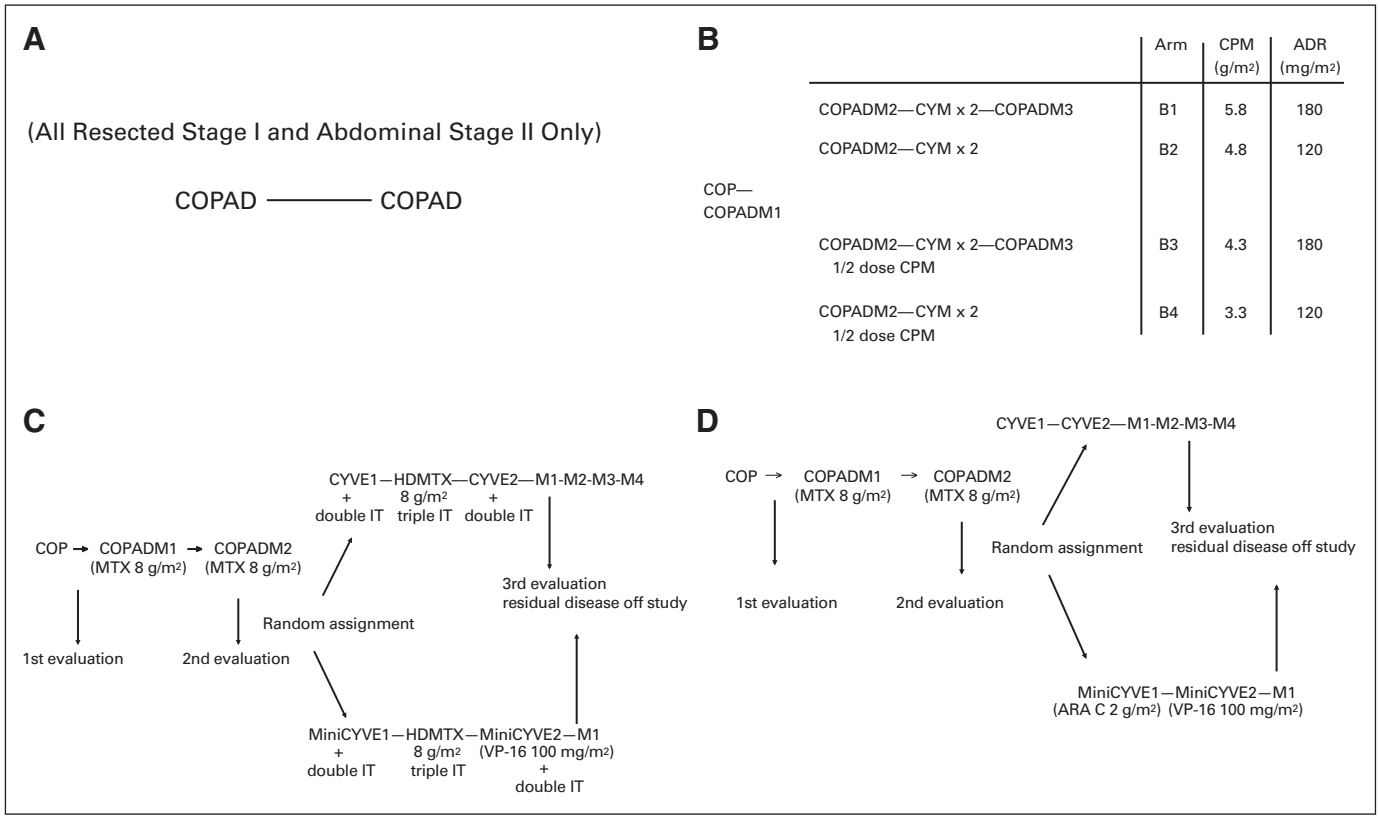

Fig 1. Overall experimental design of (A) group A therapy, (B) group B therapy, (C) group C therapy for CNS-positive patients, (D) group C therapy for CNS-negative patients. The number after the regimen name indicates the cycle number. ADR, doxorubicin; ARA C, cytarabine; COP, cyclophosphamide, vincristine, and prednisone; COPAD, cyclophosphamide, vincristine, prednisone, and doxorubicin; COPADM, COPAD with high-dose methotrexate (HD-MTX; 8 g/m^2); CPM, cyclophosphamide; CYM, cytarabine and HD-MTX; CYVE, cytarabine 2 g/m^2 and etoposide 100 mg/m^2; IT, intrathecal; M1, maintenance cycle 1; M2, maintenance cycle 2; M3, maintenance cycle 3; M4, maintenance cycle 4; VP-16, etoposide.

diagnoses were in agreement or following review on a multiheaded microscope by all members of the reviewing committee. If morphology was ambiguous between DLBCL and BL leading to discordance by the reviewers, BCL-2 and MIB-1 stains were performed to aid in diagnosis, although this was necessary in less than 10% of cases.

Statistical Methods

The primary end point for analysis was EFS, which was defined as the minimum time to death from any cause, relapse, progressive disease, second malignant neoplasm, or biopsy-positive residual disease at the end of the group C consolidation phase. The secondary end point was OS, which was the time to death from any cause measured from the start of therapy. Product-limit estimates of EFS and OS probabilities are reported along with Greenwood SEs. The log-rank test and multivariate Cox regression analysis were used to identify significant factors. All reported *P* values are two-sided. Statistical computations were performed by using STATA version 11 (STATA, College Station, TX).

RESULTS

Demographics

There were 1,111 patients registered on FAB LMB 96 from May 1996 to June 2001. There were 132, 744, and 235 patients treated on group A, group B, and group C therapy, respectively. Fifteen percent of patients (n = 166) were 15 years old or older. Patients up to age 21 were permitted on study in CCG, but not in the other cooperative groups. Thus, 21% of CCG registered patients were 15 years of age or older compared with 7% for SFOP and 13% for UKCCSG ($P < .001$). The frequency of males was 3.3 times higher than that for females in the entire cohort.

Patient demographics and disease characteristics are summarized separately for adolescents (age $\geq$ 15 years) and younger children (age $<$ 15 years) in Table 1. There was a difference in the distribution of disease site ($P < .001$) with a higher frequency of patients with abdominal/retroperitoneal and head and neck disease among younger children and a higher frequency of patients with primary mediastinal and peripheral node disease among adolescents. The distribution of pathology subtypes was also different ($P < .001$); patients with BL/BLL were more frequent among younger children although patients with DLBCL and mediastinal disease were more frequent among adolescents. There was a difference in distribution of disease stage ($P = .003$), with a higher percentage of patients younger than age 15 years in stage III. There was also a difference in distribution of BM and CNS positivity ($P = .01$), with a lower frequency of adolescents being BM-positive compared with younger children (13% *v* 22%), but frequency was similar for involvement of the CNS in the two age groups (11% *v* 10%). There was a lower proportion of patients with LDH $\geq 2 \times$ institutional upper limit of normal (ULN) among adolescents compared with children younger than age 15 years (34% *v* 45%; $P = .009$).

EFS and OS

Median follow-up in patients not experiencing an event was 4.5 years. The estimated 3-year EFS and OS in the entire cohort of patients (N = 1,111) with newly diagnosed mature B-cell NHL treated in the FAB LMB 96 study was 88% $\pm$ 1.0% and 90% $\pm$ 0.91%, respectively

Table 1. Demographic Characteristics and Risk Factors

Characteristic	Adolescents (older than age 15 years) No.	%	Children (younger than age 15 years) No.	%	*P*
Total No. of patients	166	15	945	85	
Sex					.26
Male	122	73	732	77	
Female	44	27	213	23	
Male:female ratio	2.8:1		3.4:1		.21
Prognostic group					
A	23	14	109	12	
B	116	70	628	66	
C	27	16	208	22	
Stage (Murphy)					.003
I	27	16	93	10	
II	27	16	200	21	
III	84	51	405	43	
IV	28	17	247	26	
Primary site					< .001
Peripheral node	32	19	88	9	
Mediastinal	32	19	22	2	
Abdominal/retroperitoneal	57	34	517	55	
Head and neck	13	9	177	19	
Other	32	19	141	15	
Pathology					< .001
BL/BLL	79	48	718	74	
DLBCL	75	45	174	18	
Other	12	7	53	8	
BM/CNS					.01
BM negative/CNS negative	137	83	696	74	
BM positive/CNS negative	10	6	151	16	
BM negative/CNS positive	7	4	39	4	
BM positive/CNS positive	11	7	57	6	
LDH					.009
< 2 × institutional ULN	107	66	504	55	
> 2 × institutional ULN	54	34	406	45	
Unknown	5		35		

Abbreviations: BL, Burkitt lymphoma; BLL, Burkitt-like lymphoma; DLBCL, diffuse large B-cell lymphoma; LDH, lactate dehydrogenase; ULN, upper limit of normal.

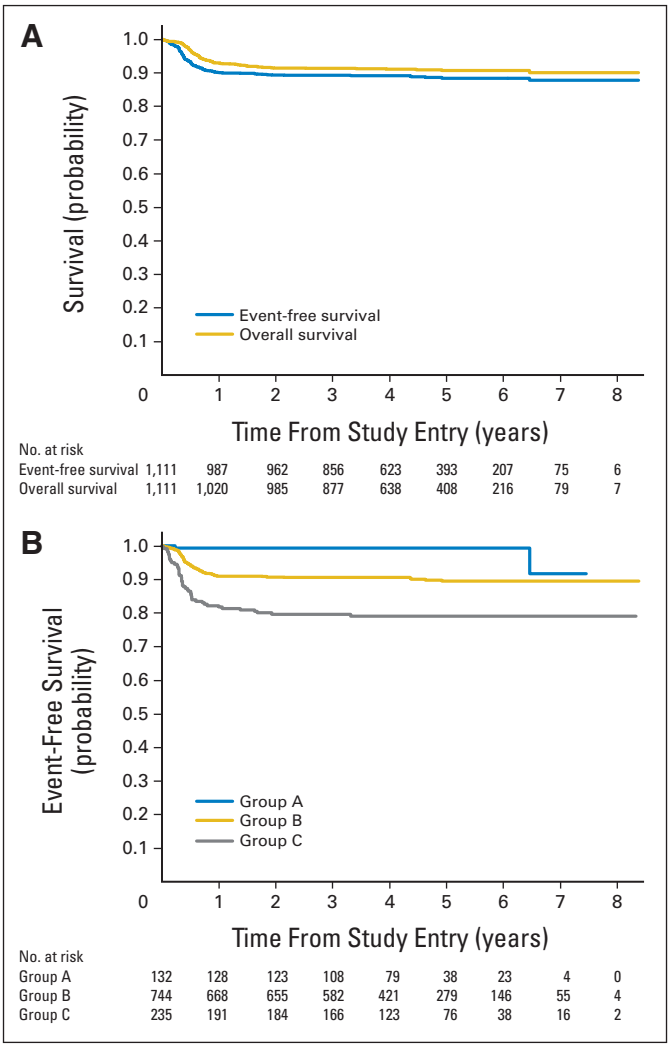

Fig 2. (A) Probability of overall survival and event-free survival of entire cohort. (B) Probability of event-free survival in patients treated with group A, group B, or group C therapy.

(Fig 2A). The estimated 3-year EFS in patients who had group A, B, and C therapy was 99% ± 0.75%, 89% ± 1.2%, and 79% ± 2.7%, respectively ($P < .001$; Fig 2B). The estimated 3-year EFS in children younger than age 15 years was similar to that of adolescent patients (89% ± 1.0% *v* 84% ± 3.4%; $P = .15$; Fig 3). There was also no significant difference in the estimated 3-year OS between the two age groups (< 15 *v* ≥ 15 to 21 years; 91% ± 0.93% *v* 85% ± 3.2%; $P = .083$).

Risk Factors for EFS

The log-rank analysis for EFS identified several risk factors that were significant, including prognostic group ($P < .001$; Fig 4A), LDH ≥ 2 × ULN ($P < .001$), BM/CNS status at diagnosis ($P < .001$, Fig 4B), stage III/IV ($P < .001$), and primary site ($P < .001$; Fig 4C).

A Cox multivariate regression analysis was performed that included age (≥ 15 *v* < 15 years), prognostic group, stage, primary site, pathology, BM/CNS involvement, and LDH ≥ 2 × ULN. The relative failure rate (RFR) estimates, confidence intervals, and *P* values from this analysis are summarized in Table 2. Age, prognostic group, stage, and pathology were not significant in this analysis. However, several other variables were significant. LDH ≥ 2 × ULN had a relative risk (RR) of 2.0 ($P = .003$). Primary site was significant ($P < .012$) primarily because of higher treatment failure rate associated with mediastinal disease and abdominal/retroperitoneal disease (RFR, 4.5 and 2.7, respectively, *v* patients with peripheral node primaries). BM-positive/CNS-positive status was significant ($P < .001$), primarily because of the higher treatment failure rate associated with combined BM and CNS involvement (RFR, 4.9 *v* patients with neither BM nor CNS involvement).

DISCUSSION

This trial was the largest multinational cooperative group study in children and adolescents with newly diagnosed mature B-cell NHL. Malignant lymphomas are the most common cancer in adolescents (age 15 to 19 years) and represent almost one in four of all malignant

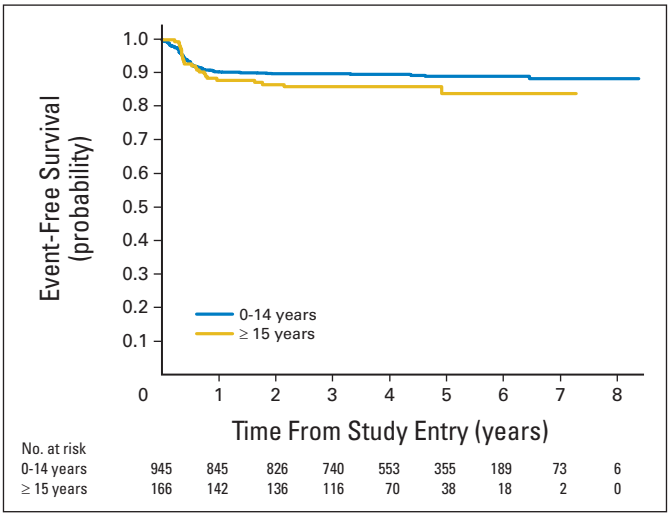

Fig 3. Probability of event-free survival in patients treated in the French-American-British Mature B-Cell Lymphoma 96 (FAB LMB 96) study, grouped by age.

tumors during in this age group.[17,25-27] Furthermore, successful treatment of adolescent cancer has been significantly hampered by several contributing factors, including labile emotional well-being, lack of parental guidance, poor participation in clinical trials, decreased medical insurance coverage, lack of economic resources, and few multidisciplinary programs.[27-29]

Historically, there was general consensus that mature B-cell NHL, especially BL, occurring in adolescence was an independent risk factor for a poorer EFS compared with that occurring in children younger than age 15 years.[9,13] In the CCG retrospective review of 470 children with BL treated from 1977 to 1994 on front-line CCG B-cell NHL trials, adolescents age ≥ 15 years had a significantly inferior survival compared with children younger than age 15 years (35% *v* 55% to 60%; $P < .002$).[9] Similarly, Patte et al[13] demonstrated in patients with intermediate-risk disease given group B therapy in LMB 89 that adolescents had an RR of 6.7 (range, 2.2 to 20.4) for relapse ($P < .006$) compared with younger patients (younger than age 15 years) with mature B-cell NHL. Burkhardt et al[26] reviewed the outcome of all adolescents with NHL treated on Berlin-Frankfurt-Münster (BFM) 86, BFM 90, and BFM 95 and demonstrated in a multivariate analysis a significantly inferior outcome in adolescents (age 15 to 18 years) with mediastinal large B-cell lymphoma ($P < .054$) and a trend in females age ≥ 15 years with DLBCL. However, our current, more intensive study demonstrated that age ≥ 15 years (adolescents) was not an independent risk factor for inferior EFS, nor was there any indication of a differential effect of age within patient subgroups defined by morphology or sex.

However, the current study did demonstrate that LDH level, mediastinal disease, and BM-positive/CNS-positive disease are independent risk factors for outcome in children and adolescents with mature B-cell NHL treated on modern, short but intensive therapy such as that in FAB LMB 96. A major risk factor identified in this study associated with an inferior outcome was primary site ($P < .012$ in multivariate analysis), especially in patients with mediastinal disease (RR of 4.5 relative to patients with peripheral node primaries). Although mediastinal disease represents less than 2% of all NHLs in

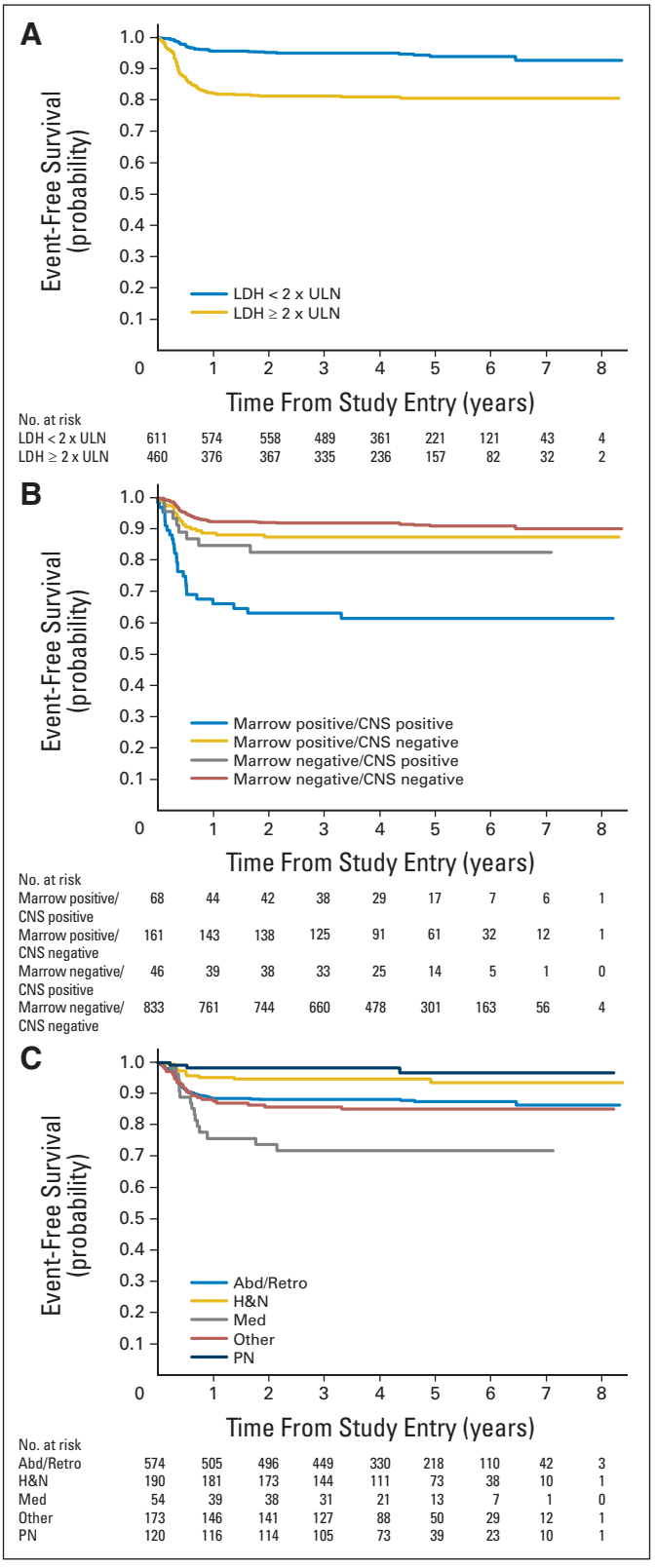

Fig 4. Probability of event-free survival in patients treated in the French-American-British Mature B-Cell Lymphoma 96 (FAB LMB 96) study, stratified by (A) lactate dehydrogenase (LDH) at diagnosis (< 2 × institutional upper limit of normal (ULN) *v* ≥ 2 × institutional ULN), (B) bone marrow (BM)/CNS involvement, and (C) primary site. Abd/retro, abdominal/retroperitoneal; H&N, head and neck; Med, mediastinal; PN, peripheral node.

Table 2. Significant Risk Factors Associated With Relapse/Progression on French-American-British Mature B-Cell Lymphoma 96 (FAB LMB 96) Study Univariate and Multivariate Analysis

Risk Factor	Univariate Analysis		Multivariate Analysis		
	3-Year EFS (% ± SE)	Log-Rank *P*	RFR	95% CI	*P*
Age, years		.15			.58
< 15	89 ± 1.0		1.0		
≥ 15	84 ± 3.4		1.2	0.70 to 1.9	
Prognostic group		< .001			.90
A	99 ± 0.75		1.0		
B	89 ± 1.2		2.0	0.38 to 11	
C	79 ± 2.7		2.6	0.36 to 19	
Stage (Murphy)		< .001			.082
I/II	98 ± 1.1		1.0		
III/IV	84 ± 1.4		2.4	0.90 to 6.4	
Primary site		< .001			.012
Peripheral node	97 ± 2.0		1.0		
Mediastinal	72 ± 6.2		4.5	1.2 to 17	
Abdominal/retroperitoneal	87 ± 1.4		2.7	0.83 to 9.0	
Head and neck	94 ± 2.0		1.2	0.32 to 4.4	
Other	85 ± 2.8		1.2	0.35 to 4.3	
Pathology		.92			.24
BL/BLL	89 ± 1.1		1.0		
DLBCL	87 ± 2.5		1.6	0.92 to 2.7	
Other	87 ± 4.2		1.0	0.49 to 2.1	
BM/CNS		< .001			< .001
BM negative/CNS negative	91 ± 1.1		1.0		
BM positive/CNS negative	88 ± 2.6		1.1	0.43 to 2.7	
BM negative/CNS positive	83 ± 5.6		1.8	0.50 to 6.6	
BM positive/CNS positive	61 ± 6.0		4.9	1.6 to 15	
LDH		< .001			.003
< 2 × institutional ULN	94 ± 1.1		1.0		
≥ 2 × institutional ULN	81 ± 1.9		2.0	1.3 to 3.2	

Abbreviations: BL, Burkitt lymphoma; BLL, Burkitt-like lymphoma; DLBCL, diffuse large B-cell lymphoma; EFS, event-free survival; RFR, relative failure rate; ULN, upper limit of normal.

children younger than age 15 years, its incidence in adolescence increases to approximately 5% to 7%.[26] In an earlier CCG study, Lones et al[23] reported a 75% EFS in children with NHL arising in the mediastinum in which the predominance and histology was PMBL. Similarly, Burkhardt et al[26] reported for the BFM, for NHL studies BFM-86, BFM-90, and BFM-95, an approximately 65% ± 8% EFS in children and adolescents with mediastinal large B-cell lymphoma. Gene expression profiles in adults with PMBL are significantly different from those of other common histologic subtypes of DLBCL.[23,30-32] These findings suggest that short but intensive mature B-cell NHL therapy without radiotherapy, such as that in the FAB LMB 96 study, may not be the optimal therapy for mediastinal disease in children and adolescents. We are currently investigating the role of systemic rituximab with FAB LMB group B therapy in children with advanced mature B-cell NHL, including those with mediastinal disease.[33,34]

Increase in LDH (≥ 2 × ULN) was also associated with a significant decrease in EFS in children and adolescents with mature B-cell NHL treated on the FAB LMB 96 trial (RR, 2.0; $P < .001$). Advanced-stage disease has previously been demonstrated by several pediatric cooperative groups, including CCG, SFOP, BFM, and the Italian Association of Pediatric Hematology Oncology (AEIOP) to be associated with an inferior outcome[7,9,13,14,35,36] In this most recent study, advanced stage was not an independent risk factor for relapse or progression. However, increased LDH at diagnosis as defined differently by different cooperative groups has been historically associated with an inferior outcome in children and adolescents with mature B-cell NHL.[7,13,14,35] Recent studies by Woessman et al[16] have demonstrated that HD-MTX (5 g/m^2) over 24- versus 4-hour infusion in patients with advanced-stage disease and/or increased LDH levels at diagnosis in children and adolescents with mature B-cell NHL treated on BFM NHL 95 is superior and is associated with a 93% EFS. Similarly, the addition of rituximab to the FAB MB B4 chemotherapy backbone in children and adolescents with mature B-cell NHL with advanced-stage disease with or without increased LDH levels is safe and well-tolerated.[33,34] Recently, Meinhardt et al[37] reported good response rates with rituximab in children with intermediate and advanced mature B-cell NHL in a single-dose phase II window design. Randomized and prospective studies will be required to determine whether these and other strategies will significantly increase the EFS in children and adolescents with newly diagnosed advanced-stage mature B-cell NHL and/or with increased LDH levels at diagnosis.

In summary, this large and prospective FAB LMB 96 trial in children and adolescents with newly diagnosed mature B-cell NHL demonstrated that adolescent age (≥ 15 years) is not an independent risk factor for inferior outcome in either univariate or multivariate analysis. Further, increased LDH level (≥ 2 × institutional ULN), mediastinal disease, and combined BM and CNS disease at diagnosis were each independently associated with an increased risk of treatment failure in children and adolescents with mature B-cell NHL who were treated with modern, short but intensive therapy such as that in the FAB LMB 96 study. Other biologic features such as cytogenetics and/or molecular genetics and/or minimal residual disease may also be associated with an increased risk of treatment failure in children and adolescents with mature B-cell NHL.[36,38] Future studies will be required to determine whether different therapeutic strategies can overcome the poor prognostic risk factors discussed herein in children and adolescents with mature B-cell NHL. The results of this analysis will hopefully form the basis of the next risk-adapted childhood and adolescent mature B-cell NHL study.

AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

The author(s) indicated no potential conflicts of interest.

AUTHOR CONTRIBUTIONS

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Final approval of manuscript: All authors

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ORIGINAL REPORT

Randomized Phase III Study Comparing Paclitaxel/Cisplatin/Gemcitabine and Gemcitabine/Cisplatin in Patients With Locally Advanced or Metastatic Urothelial Cancer Without Prior Systemic Therapy: EORTC Intergroup Study 30987

Joaquim Bellmunt, Hans von der Maase, Graham M. Mead, Iwona Skoneczna, Maria De Santis, Gedske Daugaard, Andreas Boehle, Christine Chevreau, Luis Paz-Ares, Leslie R. Laufman, Eric Winquist, Derek Raghavan, Sandrine Marreaud, Sandra Collette, Richard Sylvester, and Ronald de Wit

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ABSTRACT

Purpose
The combination of gemcitabine plus cisplatin (GC) is a standard regimen in patients with locally advanced or metastatic urothelial cancer. A phase I/II study suggested that a three-drug regimen that included paclitaxel had greater antitumor activity and might improve survival.

Patients and Methods
We conducted a randomized phase III study to compare paclitaxel/cisplatin/gemcitabine (PCG) with GC in patients with locally advanced or metastatic urothelial carcinoma. Primary outcome was overall survival (OS). Secondary outcomes were progression-free survival (PFS), overall response rate, and toxicity.

Results
From 2001 to 2004, 626 patients were randomly assigned; 312 patients were assigned to PCG, and 314 patients were assigned to GC. After a median follow-up of 4.6 years, the median OS was 15.8 months on PCG versus 12.7 months on GC (hazard ratio [HR], 0.85; $P = .075$). OS in the subgroup of all eligible patients was significantly longer on PCG (3.2 months; HR, 0.82; $P = .03$), as was the case in patients with bladder primary tumors. PFS was not significantly longer on PCG (HR, 0.87; $P = .11$). Overall response rate was 55.5% on PCG and 43.6% on GC ($P = .0031$). Both treatments were well tolerated, with more thrombocytopenia and bleeding on GC than PCG (11.4% *v* 6.8%, respectively; $P = .05$) and more febrile neutropenia on PCG than GC (13.2% *v* 4.3%, respectively; $P < .001$).

Conclusion
The addition of paclitaxel to GC provides a higher response rate and a 3.1-month survival benefit that did not reach statistical significance. Novel approaches will be required to obtain major improvements in survival of incurable urothelial cancer.

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INTRODUCTION

Untreated metastatic urothelial carcinoma is associated with a median survival time rarely exceeding 3 to 6 months. It is a chemotherapy-sensitive tumor, and cisplatin-based chemotherapy is the standard treatment.[1,2] Historically, the combination of methotrexate, vinblastine, doxorubicin, and cisplatin (MVAC) modestly improved survival compared with cisplatin alone[3]; the combination of cyclophosphamide, doxorubicin, and cisplatin[4]; and a carboplatin-based regimen.[5] However, dose intensification of MVAC did not improve median survival,[6-8] and the disappointing long-term outcome with available regimens has led to the search for new active drugs.

Among the agents assessed, the microtubule-stabilizing taxane paclitaxel (Taxol; Bristol-Myers Squibb, Princeton, NJ) and the pyrimidine antimetabolite gemcitabine (Gemzar; Eli Lilly, Indianapolis, IN) have demonstrated high single-agent activity in patients with advanced urothelial cancer. In previously untreated patients, paclitaxel produced a response rate of 42%, with a 27% complete response rate.[9] Gemcitabine has single-agent activity against urothelial cancer in previously treated

and untreated patients, with overall response rates in the range of 24% to 28%.[10-13]

The encouraging results with gemcitabine led to a phase III trial comparing a combination of gemcitabine and cisplatin (GC) with MVAC.[2] GC provided a similar survival compared with MVAC with a better safety profile and tolerability. This favorable risk-benefit ratio established GC as another standard option for patients with locally advanced and metastatic transitional-cell carcinoma.

Given the different mechanisms of action and the partially nonoverlapping toxicity profiles of cisplatin, gemcitabine, and paclitaxel, the triple combination was assessed by the Spanish Oncology Genitourinary Group.[14,15] In 58 patients with advanced urothelial tumors in the combined phase I/II cohort, the overall response rate was 77.6% (95% CI, 60% to 98%). There were 16 complete responses (27.6%), and the median survival time was 15.6 months.[14,15] Thus, the three-drug combination was feasible, and the median survival seemed superior to that obtained with the standard MVAC regimen.[2] Therefore, the European Organisation for Research and Treatment of Cancer (EORTC) designed a phase III study (EORTC Intergroup Study 30987) to compare the efficacy of GC plus paclitaxel (PCG) with GC alone in patients with locally advanced or metastatic urothelial cancer. Preliminary data from this study, with a median follow-up of 3.4 years, were presented at the 43rd Annual Meeting of the American Society of Clinical Oncology in 2007[16]; this article presents the final mature results after a median follow-up of 4.6 years.

PATIENTS AND METHODS

Design

An open-label randomized, phase III intergroup study was conducted within the framework of the EORTC Genitourinary Group, with the cooperation of the German Association of Urologic Oncology, Groupe d'Etude des Tumeurs Uro-Génitales, National Cancer Institute of Canada Clinical Trials Group, Spanish Oncology Genitourinary Group, Southwest Oncology Group, and the National Cancer Research Institute Bladder Clinical Studies Group.

Eligibility

Eligible patients had histologically confirmed stage IV locally advanced (T4b, any N; or any T, N2-3) or metastatic transitional-cell carcinoma of the urothelium (pure or mixed). Tumor sites included the bladder, urethra, ureter, and renal pelvis. Patients were required to have measurable or nonmeasurable (evaluable) disease according to RECIST,[17,18] age $\geq$ 18 years, WHO performance status of 0 or 1, and a life expectancy of at least 12 weeks. Patients who received prior systemic chemotherapy or investigational agents were not allowed to enter the study. Other inclusion criteria were adequate hematologic (WBC count $\geq 3.0 \times 10^9$/L, platelet count $\geq 100 \times 10^9$/L, and hemoglobin $\geq$ 10 g/dL or 6.2 mmol/L), hepatic (serum bilirubin level $< 1.25\times$ above the normal range, ALT or AST $< 2.5\times$ above the normal range), and renal (creatinine clearance $\geq$ 60 mL/min) function. Patients with significant cardiac disease, brain metastases, or peripheral neuropathy greater than grade 2 were not eligible. Patients with a secondary primary malignancy, except for in situ carcinoma of the cervix, basal cell carcinoma of the skin, or incidental prostate cancer (T1, Gleason score $\leq$ 6, prostate-specific antigen $<$ 0.5 ng/mL), were also not eligible.

The study was conducted in accordance with the Declaration of Helsinki and Good Clinical Practice Guidelines. The study protocol was approved by the institutional review board of each participating center, and relevant patient safeguards were observed. All patients provided written informed consent.

Treatment Schedule

Patients were centrally randomly assigned at the EORTC to receive either PCG (experimental arm) or GC (control arm). Random assignment was stratified by study site, WHO performance status (0 *v* 1), and the presence or absence of metastatic disease. Treatment schedule and dose adjustments were done according to previously published data.[2] In summary, in the GC arm, gemcitabine 1,000 mg/m^2 was administered on days 1, 8, and 15, and cisplatin 70 mg/m^2 was administered on day 2, every 28 days. The PCG arm consisted of

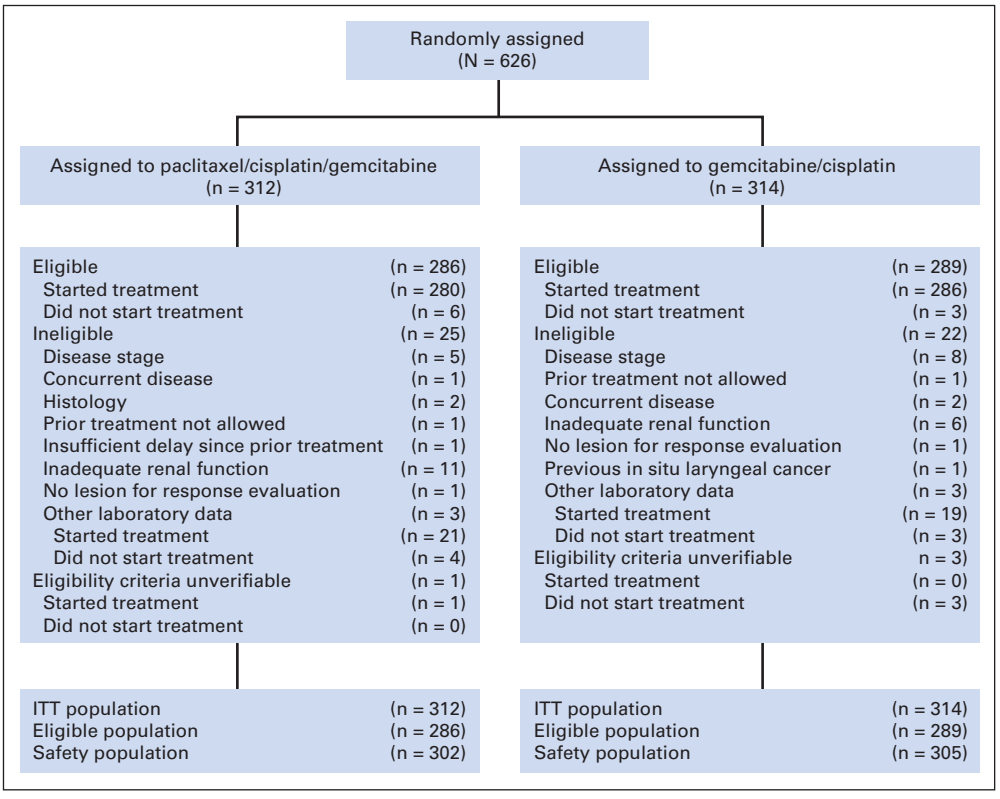

Fig 1. Flow chart of the study population. Eligibility before the database lock was assessed by the study coordinator (J.B.) and thereafter reviewed by the statisticians (R.S. and S.C.) and the clinical research physician (S.M.). ITT, intent to treat.

the sequential administration of paclitaxel 80 mg/m^2 before the same doses of gemcitabine and paclitaxel as in the GC arm on day 1. Paclitaxel and gemcitabine were administered at the same doses on day 8. Cycles were repeated every 21 days. Patients were treated for a maximum of six cycles or until documentation of progression according to RECIST,[17] unacceptable toxicity, or a request for discontinuation by the patient or attending physician.

Study End Points

The primary end point was overall survival (OS), which was defined as the time between random assignment and death from any cause. Secondary end points were progression-free survival, response rate according to RECIST,[17] and toxicity using the National Cancer Institute Common Toxicity Criteria (CTC) version 2.0. Patients were assessable for response if they had evaluable disease (measurable and/or non measurable), had received at least one cycle, and had at least one follow-up tumor assessment. Response had to be confirmed after at least 4w. Patients were evaluated every 3m during the first 2y and every 6m thereafter.

Statistical Considerations

The median survival on GC was assumed to be 14 months. The trial was designed to detect an increase in the median survival from 14 months to 18 months on PCG (or equivalently an increase in the 14 month survival rate from 50% to 58.7%), which corresponds to a hazard ratio (HR) of 0.778. It was estimated that a total of 610 patients (305 patients in each arm) was needed to observe the 498 deaths required based on a two-sided log-rank test at error rates of $\alpha = .05$ and $\beta = .20$. Two interim efficacy analyses were carried out in January 2004 and June 2007. To maintain the overall α at 5%, the significance level used for the final analysis was 3.9%.

The primary analysis was carried out in the intent-to-treat (ITT) population of all randomly assigned patients. Time-to-event curves (duration of OS and PFS) were estimated using the Kaplan-Meier method and compared based on a two-sided log-rank test. Response rates were compared using a χ^2 test. Survival was also compared in the eligible patients (unplanned, post hoc analysis).

RESULTS

Between May 2001 and June 2004, 626 patients from 137 institutions were randomly assigned, 314 patients to GC and 312 patients to PCG. The 607 patients who started treatment were included in the safety analyses. Forty-seven patients (22 patients on GC and 25 patients on PCG) were ineligible, with an additional four patients with eligibility unverifiable, 41 of whom started protocol treatment (Fig 1).

Patient Characteristics

Patient characteristics at random assignment were well balanced between the arms. Baseline data are listed in Table 1.

Table 1. Patient Demographics and Disease Characteristics at Random Assignment

Demographic or Characteristic	Paclitaxel/ Cisplatin/ Gemcitabine (n = 312) No. of Patients	%	Gemcitabine/ Cisplatin (n = 314) No. of Patients	%	Total (N = 626) No. of Patients	%
Sex						
Male	256	82.3	252	81.0	508	81.7
Female	55	17.7	59	19.0	114	18.3
Age, years						
Median	61		61		61	
Range	27-80		32-79		27-80	
WHO performance status						
0	171	54.8	171	54.5	342	54.6
1	141	45.2	143	45.5	453	45.5
Location of primary tumor						
Bladder	254	81.4	259	82.5	513	81.9
Renal pelvis	27	8.6	25	8.0	52	8.3
Ureter	13	4.2	17	5.4	30	4.8
Urethra	11	3.5	8	2.5	19	3.0
Other	6*	1.9	2†	0.6	8	1.3
Distant metastases	275	88.1	276	87.9	551	88.0
Nonvisceral metastases	130	41.7	121	38.5	251	40.1
Visceral metastases‡	145	46.5	155	49.4	300	47.9
Bone	51	16.3	57	18.2	108	17.3
Liver	41	13.1	51	16.2	92	14.7
Lung	70	22.4	84	26.8	154	24.6
Peritoneum	19	6.1	12	3.8	31	5.0
No. of metastatic sites						
1	108	34.6	110	35.0	218	34.8
2	86	27.6	89	28.3	175	28.0
≥ 3	81	26.0	77	24.5	158	25.2
Prognostic risk group§						
Low	98	31.4	93	29.6	191	30.5
Intermediate	136	43.6	135	43.0	271	43.3
High	77	24.7	83	26.4	160	25.6

Abbreviations: GC, gemcitabine + cisplatin; PCG, paclitaxel/cisplatin/gemcitabine.
*One patient missing data.
†Three patients missing data.
‡CNS: 1 patient on PCG and 0 on GC; bone marrow: 0 patients on PCG and 2 on GC.
§Based on Bajorin et al.[19]

Survival

After a median follow-up of 4.6 years (maximum, 6.8 years), 504 patients (80.5%) have died, 256 (81.5%) on GC and 248 (79.5%) on PCG. Causes of death were urothelial cancer in 434 patients (226 patients [72%] on GC and 208 patients [66.7%] on PCG), toxicity in nine patients, chronic disease in one patient, other causes in 36 patients, and unknown in 24 patients.

The median OS was 3.1 months longer in the PCG arm; median OS was 15.8 months (95% CI, 13.6 to 17.5 months) on PCG compared with 12.7 months (95% CI, 11.0 to 14.4 months) on GC. However, the difference in median OS did not reach statistical significance (HR, 0.85; 95% CI, 0.72 to 1.02; $P = .075$; Fig 2). The OS rates at 1 and 4 years were 61.4% (95% CI, 55.7% to 66.6%) and 17.2% (95% CI, 13.0% to 21.8%), respectively, on PCG, compared with 52.8% (95% CI, 47.0% to 58.2%) and 16.4% (95% CI, 12.3% to 20.9%), respectively on CG. Results were similar when adjusted simultaneously by cooperative group, WHO performance status, and presence or absence of metastatic disease.

All eligibility criteria including laboratory values were checked according to the most recent information available at the time of random assignment. Forty-seven patients (8%) were ineligible, mostly for reasons of disease stage and/or impaired renal function. Ten of these patients did not start the allocated treatment or were not physically fit enough to receive optimal treatment. Hence, we also analyzed OS in the eligible patient population, which showed that patients treated with the triplet had a significantly longer duration of survival (median, 15.9 months; 95% CI, 13.6 to 18.1 months) than patients in the GC arm (median, 12.7 months; 95% CI, 11.4 to 14.4 months; HR, 0.82; 95% CI, 0.68 to 0.98; $P = .03$; Fig 3).

After recent reports that outcome in tumors of the upper urinary tract may differ from outcome in tumors of the lower tract,[20] the

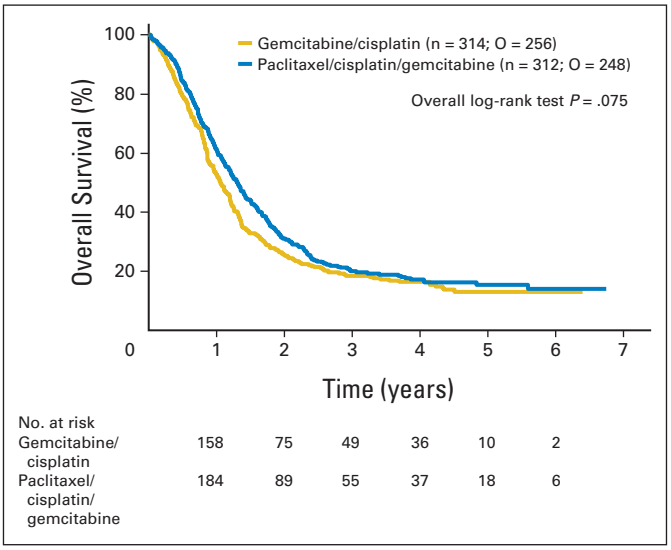

Fig 2. Overall duration of survival in the intent-to-treat patient population. O, number of observed events.

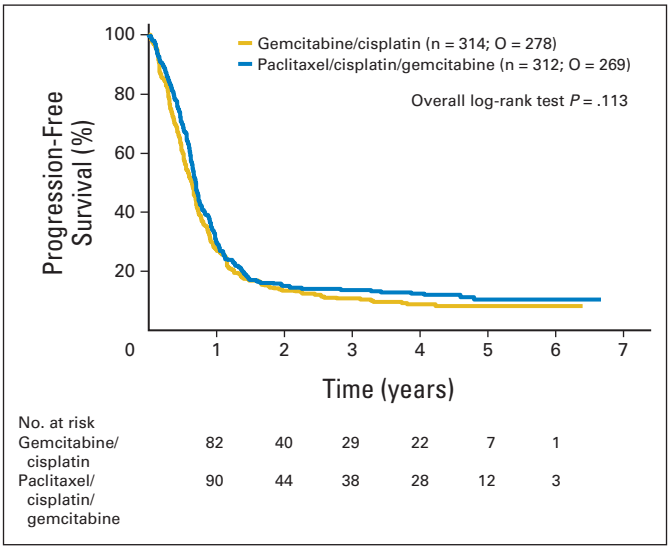

Fig 4. Duration of progression-free survival. O, number of observed events.

possible influence of anatomic site on treatment effect was investigated in an analysis that was not preplanned. Among the 81% of patients in whom the bladder was the site of the primary tumor, median OS after PCG was significantly longer than that after GC (15.9 *v* 11.9 months, respectively; HR, 0.80; 95% CI, 0.66 to 0.97; $P = .025$).

Prognostic factor analyses in the ITT population, independent of the treatment administered, showed statistically significant differences in survival according to WHO performance status (1 *v* 0: HR, 1.50; 95% CI, 1.26 to 1.79; $P < .001$), metastatic disease (presence *v* absence: HR, 1.38; 95% CI, 1.13 to 1.69; $P = .001$), visceral metastases (presence *v* absence; HR, 1.74; 95% CI, 1.46 to 2.08; $P < .001$), and number of Memorial Sloan-Kettering Cancer Center risk factors (two risk factors *v* no or one risk factor: HR, 2.17; 95% CI, 1.79 to 2.64; $P < .001$).

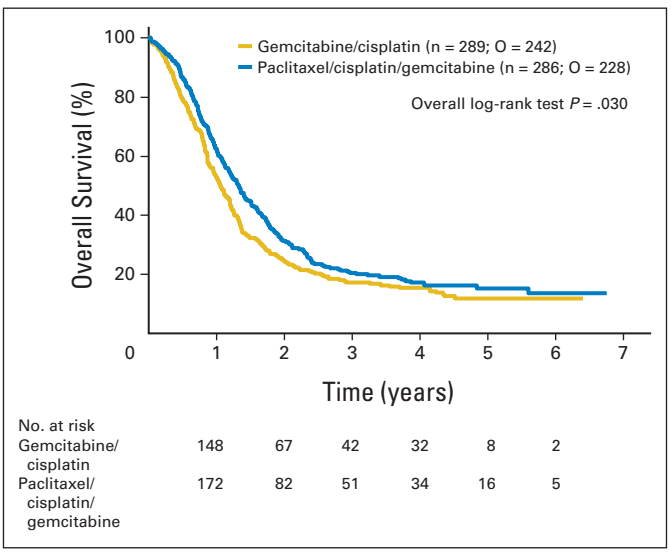

Fig 3. Overall duration of survival in the eligible patients. O, number of observed events.

PFS

Progression or death was documented in 547 patients, 278 on GC and 269 on PCG. The median PFS was 8.3 months on PCG and 7.6 months on GC (HR, 0.87; 95% CI, 0.74 to 1.03; $P = .113$; Fig 4).

Response Rate

The overall response rate (complete or partial; blinded review by J.B.) was significantly higher among patients treated with PCG than GC (55.5% *v* 43.6%, respectively; $P = .0031$). Response to treatment is shown in Table 2. Overall, 48 patients (21 patients in the PCG arm and 27 patients in the GC arm) underwent postchemotherapy surgical resection.

Drug Exposure and Toxicity

Of the 626 randomly assigned patients, 607 started the protocol treatment, 302 on PCG and 305 on GC (three patients refused, three patients had disease progression before start, four patients had other complicating diseases, four patients had other reasons, and information was lacking in five patients). The median duration of treatment

Table 2. Overall Response According to RECIST

Best Overall Response to Treatment	Paclitaxel/ Cisplatin/ Gemcitabine (n = 312)		Gemcitabine/ Cisplatin (n = 314)		Total (N = 626)	
	No. of Patients	%	No. of Patients	%	No. of Patients	%
Complete response	42	13.5	35	11.1	77	12.3
Partial response	131	42.0	102	32.5	233	37.2
Stable disease	69	22.1	97	30.9	166	26.5
Progression of disease	21	6.7	47	15.0	68	10.9
Early death	8	2.6	7	2.2	15	2.4
Not assessable	31	9.9	17	5.4	48	7.7
Treatment never started	10	3.2	9	2.9	19	3.0

Table 3. Nonhematologic and Hematologic Adverse Events

Adverse Event	Gemcitabine/Cisplatin (n = 305)				Paclitaxel/Cisplatin/Gemcitabine (n = 302)			
	Grade 3		Grade 4		Grade 3		Grade 4	
	No. of Patients	%	No. of Patients	%	No. of Patients	%	No. of Patients	%
Nonhematologic adverse events								
Vomiting	19	6.2	1	0.3	20	6.6	1	0.3
Pulmonary toxicity	12	3.9	3	1.0	12	4.0	4	1.3
Cardiovascular events*	36	11.8	7	2.3	28	9.3	5	1.6
Allergy	0	0	1	0.3	5	1.7	4	1.3
Fatigue	34	11.1	0		43	14.2	4	1.3
Bleeding	22	7.0	1	0.3	9	2.9	1	0.3
Infection	40	13.1	4	1.3	49	16.2	8	2.6
Renal toxicity	10	3.3	5	1.6	11	3.6	3	1.0
Neuropathy/sensory	1	0.3	0	0	0	0	1	0.3
Alopecia	2	0.7	0	0	5	1.7	0	0
Diarrhea	10	3.3	1	0.3	14	4.6	0	0
Hematologic adverse events								
WBC	102	33.4	16	5.2	102	33.8	53	17.5
Neutropenia	93	30.5	61	20.0	86	28.5	108	35.8
Thrombocytopenia	140	45.9	19	6.2	92	30.5	12	4.0
Hemoglobin	70	23.0	8	2.6	60	19.9	8	2.6

*Includes edema, hypotension, thrombosis/embolism, and other cardiovascular events.

was 16.3 weeks (range, 0.1 to 219 weeks). Appendix Table A1 (online only) lists treatment duration, dose reduction, and discontinuation.

Overall, the addition of paclitaxel to the combination of GC had little effect on the frequency or severity of toxic effects. Details of nonhematologic and hematologic adverse events are listed in Table 3.

Patients on the PCG arm, compared with patients on the GC arm, experienced more grade 4 neutropenia (35.8% *v* 20%, respectively; $P <$ .001), more febrile neutropenia (13.2% *v* 4.3%, respectively; $P <$ .001), and a greater need for granulocyte colony-stimulating factor administration (17% *v* 11%, respectively; $P = .03$). However, there was no difference between treatments in the occurrence of neutropenic sepsis. Grade 4 thrombocytopenia was more frequent in the GC arm versus the PCG arm (6.2% *v* 4.0%, respectively; $P = .03$). Grade 3 or 4 thrombocytopenia associated with grade 3 bleeding was also more frequent in the GC arm than the PCG arm (11.4% *v* 6.8%, respectively; $P = .05$).

Severe acute toxicity (toxic death, grade 3 or 4 thrombocytopenia with grade 3 or 4 hemorrhage, grade 4 thrombocytopenia with hemorrhage, grade 3 asthenia at first cycle, grade 4 asthenia during treatment, grade 3 or 4 renal toxicity, grade 3 or 4 neutropenic fever, or grade 3 or 4 mucositis) was observed in 20.2% of patients on PCG (including six toxic deaths) and in 14.8% of patients on GC (including three toxic deaths).

DISCUSSION

This large, multinational, intergroup, phase III study, to our knowledge the largest study ever conducted in locally advanced or metastatic urothelial carcinoma, enrolling more than 600 patients over 3 years, confirms that cooperative groups on two continents can work together to provide timely answers to important clinical questions in this disease. The study shows that the three-drug combination of PCG provides a better response rate and a 3.1-month prolongation in median survival when compared with standard GC alone. The 15.8-month median OS on the triplet in this trial closely matches the outcome in the phase II study.[14,15] The present findings also confirm the tolerability of the PCG regimen.

The trial was designed to detect a difference of 4 months in median survival between GC and PCG. The choice of 4 months was driven by the expected median survival of 18 months initially obtained in the phase I/II dose-finding study.[15] The phase III study reported here showed a difference of 3.1 months in the OS in the ITT population, which is a strong trend but did not reach statistical significance. In view of the potential dilution effect of 8% ineligible patients, some of whom either did not receive the allocated treatment or were not physically fit enough to receive optimal treatment, we also carried out an analysis in the 575 eligible patients, which showed a median survival advantage of 3.2 months favoring the triplet compared with GC (15.93 *v* 12.71 months, respectively) and a reduction of 18% in the risk of death (HR, 0.82), which did reach statistical significance ($P = .030$). The eligibility was assessed based on measurements taken before random assignment so exclusion of the ineligible patients does not bias the treatment comparison, even though this has the limitation of being an additional unplanned analysis. The planned requisite of a 4-month difference in the median duration of survival based on those data was highly ambitious.[15] The fact that the effect sought in the ITT patient population was not attained cannot be attributed to prerandomization differences in prognostic factors between the treatment groups because the two arms were generally well balanced regarding performance status and visceral metastases. This was further demonstrated in the ITT population because the conclusions were not affected after adjusting for these variables.

In addition, the trial has raised an intriguing issue of wide clinical importance. In a post hoc analysis, there was evidence of a greater and

statistically significant survival benefit in patients with bladder primaries receiving the triple regimen (median, 15.9 months for PCG *v* 11.9 months for GC) in contrast to patients with nonbladder primaries, in whom there was no benefit. Pathologic findings in large series of upper tract urothelial cancer reveal that these tumors tend to have higher grade and stage than bladder cancer.[20] Despite morphologic similarities, there are genetic and epigenetic differences between transitional-cell carcinoma in the upper and lower urinary tracts. First, embryologically, the urothelium of bladder and ureter arises from different tissues.[21] Second, in vitro studies have shown that urothelium from the two sites differs in uroplakin content, keratin expression pattern, growth potential, and propensity to keratinize.[22] Extracellular matrix–associated proteins with counter-adhesive properties respond differently in ureteric and bladder urothelial cells.[23] Mono- and dinucleotide microsatellite instability, a feature of tumors with deficient mismatch repair, is more common in upper than lower urinary tract cancers,[24,25] and these tumors have more extensive methylation than bladder cancers.[26] To our knowledge, this study is the first to show a trend in OS advantage in a subgroup of patients with advanced urothelial cancer with bladder being the primary origin. The fact that the benefit by the triplet seems to be obtained particularly in bladder urothelial cancer and that upper tract urothelial cancer may be less responsive to chemotherapy implies that patients with bladder primaries (by far the most common site of urothelial cancer) should perhaps be treated differently from patients with urothelial tumors arising at other sites. Consequently, in the future, trials will need to prospectively analyze this hypothesis in addition to testing the importance of methylating patterns and other molecular factors.

Finally, the present results are consistent with previous findings and confirm that the GC schedule as studied in the randomized phase III study of GC versus MVAC[2] may be more toxic in terms of grade 4 thrombocytopenia than most clinicians expect, often resulting in the need for omission of gemcitabine on day 15. Newer regimens with GC using a 21-day schedule are being developed to reduce the need to administer gemcitabine on day 15, which often requires adjustment because of high hematologic toxicity.

The modest survival benefit for the combination of PCG observed in this report has been shown in an exploratory analysis in the eligible patients. The eligible patient population corresponds to the population targeted by the protocol and to whom the results are to be generalized, and therefore, this might be considered to be a more meaningful analysis. In the future, to select patients most likely to benefit from the triple therapy, the development of biomarkers that predict outcome or sensitivity to chemotherapy is an essential first step. Pharmacogenomics and genomics might eventually play a role in the selection of better candidates for treatment and aid in the personalized design of treatment.

In conclusion, this large, multinational, phase III trial in patients with locally advanced or metastatic urothelial cancer without prior systemic therapy shows that the triple combination of PCG provides a higher response rate when compared with GC. The predefined primary end point for OS improvement was not reached in the overall patient population, but the 3.2-month survival difference in the population of all eligible patients reached statistical significance. Moreover, a benefit in patients with a bladder primary was also observed in an analysis that was not preplanned. Finally, the triple combination was not appreciably more toxic than the GC regimen in this population. Ongoing studies may assist to identify patients who will derive the most benefit of taxane-based triple chemotherapy. Novel strategies will be required to have a major impact on survival in this disease.

AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

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SPECIAL ARTICLE

The 39th David A. Karnofsky Lecture: Bench-to-Bedside Translation of Targeted Therapies in Multiple Myeloma

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ABSTRACT

Multiple myeloma (MM) is a remarkable example of rapid bench-to-bedside translation in new drug development. The proteasome inhibitor bortezomib and immunomodulatory drug lenalidomide targeted MM cells in the bone marrow (BM) microenvironment to overcome conventional drug resistance in laboratory and animal models and were rapidly translated into clinical trials demonstrating their efficacy in patients with relapsed and then newly diagnosed MM, with a doubling of the median survival as a direct result. The future is even brighter. First, immune-based therapies are being developed (eg, elotuzumab monoclonal antibody [MoAb]; CD138DM immunotoxin; MM cell–dendritic cell vaccines; CD138, CS-1, and XBP-1 peptide vaccines; anti-17 MoAb; and other treatments to overcome causes of immune dysfunction). Second, promising next-generation agents target the MM cell in its microenvironment (eg, deubiquitinating enzyme inhibitors; chymotryptic [carfilzomib, Onyx 0912, MLN 9708] and broader [NPI-0052] proteasome inhibitors; immunoproteasome inhibitors; and pomalidamide). Moreover, agents targeting bone biology (eg, zoledronic acid, anti–DKK-1 MoAb, anti–B-cell activating factor MoAb and bortezomib, Btk inhibitor) show promise not only in preserving bone integrity but also against MM. Third, rationally based combination therapies, including bortezomib with Akt, mammalian target of rapamycin, or histone deacetylase inhibitors, are active even in bortezomib-refractory MM. Finally, genomics is currently being used in the definition of MM heterogeneity, new target discovery, and development of personalized therapy. Myeloma therefore represents a paradigm for targeting the tumor in its microenvironment, which has already markedly improved patient outcome in MM and has great potential in other hematologic malignancies and solid tumors as well.

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INTRODUCTION

Multiple myeloma (MM) is characterized by excess monoclonal plasma cells in the bone marrow (BM), in most cases associated with monoclonal protein in blood and/or urine. With the use of combined melphalan and prednisone nearly 50 years ago, median patient survival of patients with MM was extended to 2 to 3 years. Originally pioneered by Tim McElwain in the 1970s, high-dose melphalan followed by BM transplantation in the 1980s and with peripheral blood stem-cell rescue in the 1990s further increased patient median survival to 3 to 4 years. Since 1998, MM has represented a new paradigm in drug development because of the remarkable therapeutic efficacy of targeting tumor cells in their microenvironments.[1,2] In particular, the observation that proteasome inhibitor bortezomib and immunomodulatory drugs (IMiDs) thalidomide and lenalidomide target the MM cell in the BM microenvironment has rapidly translated from bench to bedside and six new US Food and Drug Administration–approved treatments in the past 7 years, with a doubling of patient survival from 3 to 4 to 7 to 8 years as a direct result.[3] Our contributions have been in the areas of identifying novel targets in the tumor and microenvironment, validating inhibitors directed at these targets, and conducting clinical trials leading to their approval. These collaborative efforts have included basic and clinical investigators, the pharmaceutical industry, the National Cancer Institute, US Food and Drug Administration regulators, and patient advocacy groups, with a common focus and inspired by the sole goal of improving MM treatments.[4] Indeed, the use of novel targeted inhibitors to treat relapsed refractory MM, relapsed MM, and newly diagnosed MM and most recently as consolidation and maintenance therapies has totally transformed MM therapy and patient outcome.

I have been carrying out bench-to-bedside research in MM for 38 years now, initially inspired by my mentor, Dr Richard L. Humphrey, who taught me the two most important lessons that have shaped my research and clinical practice. As a

medical student at Johns Hopkins, he instilled in me the opportunity in MM to "make science count for patients" by developing laboratory and animal models of disease and then rapidly translating promising leads from the bench to the bedside in clinical trials. Moreover, he imprinted in me the importance of treating patients as family. He has served as my inspiration and role model ever since.

DEVELOPMENT OF IMMUNE-BASED THERAPIES

After an introduction to MM both in the laboratory and clinic at Johns Hopkins during my medical school and internal medicine training, I moved to the Dana-Farber Cancer Institute for training in medical oncology, hematology, and tumor immunology. There Drs George Canellos and Robert Mayer instilled in me the importance of clinical investigation. Under the tutelage of Drs Lee Nadler and Stuart Schlossman, I was part of a team that developed monoclonal antibodies (MoAbs) directed at B-cell malignancies, including MM.[5,6] It was an extraordinary time, because these MoAbs allowed for identification of the lineage and stage of differentiation of B-cell malignancies as well as comparison of the neoplastic B cell with its normal cellular counterpart. A panel of B-cell MoAbs was useful to complement histopathologic diagnosis and identify non–T-cell acute lymphoblastic leukemia, chronic lymphocytic leukemia and lymphomas, and MM as tumors corresponding to pre–B cells, isotype diversity B differentiative stages, and plasma cells, respectively.[5]

Right from the outset, these MoAbs were also used in innovative treatment strategies in MM, and our efforts to develop immune-based MoAb and immunotoxin therapies, tumor vaccines, and mechanisms to abrogate host immunosuppression continue to the present. Specifically, high-dose therapy and autologous BM transplantation achieved remarkable extent and frequency of response, and early on, we examined whether cocktails of MoAbs (eg, CD10, CD20, PCA-1) could purge MM cells from autografts ex vivo before autologous BM transplantation.[7] Although effective at purging two to three logs of MM cells, impact on overall outcome was unaffected, likely because of residual systemic tumor burden. T cell (CD6) –directed MoAb was used to purge T cells from allogeneic BM grafts to abrogate graft-versus-host disease.[8] However, the transplant-related mortality of allotransplantation in MM remains unacceptably high to the present, and we continue to carry out studies to identify targets of allogeneic graft-versus-myeloma effect[9] and clinical protocols of nonmyeloablative allografting to exploit graft-versus-myeloma effect while avoiding attendant toxicity. Over many years, we have continued to carry out preclinical and clinical studies of MoAbs targeting MM cells, tumor-host interactions, and cytokines as well as evaluated MoAb-based immunotoxin therapies[1,10,11] (Fig 1). For example, we identified CS-1 to be highly and uniformly expressed at the gene and protein levels in patient MM cells and then showed that targeting this antigen with elotuzumab was effective in preclinical models of MM in the BM milieu both in vitro and in vivo.[13] These promising data in turn led to a clinical trial of elotuzumab, which achieved stable disease in relapsed refractory MM but did not induce responses sufficient to warrant new drug development. Importantly, our preclinical studies showed that lenalidomide enhanced antibody-dependent cellular cytotoxicity triggered by elotuzumab,[13] providing the rationale for a combination clinical trial with promising results. This bedside-to-bench-and-back iterative process illustrates our translational focus. An example of an immunotoxin clinical trial is that of CD138 linked to maytansonoid toxin DM, which is currently ongoing based on our promising data both in vitro and in xenograft models of human MM in mice.[14]

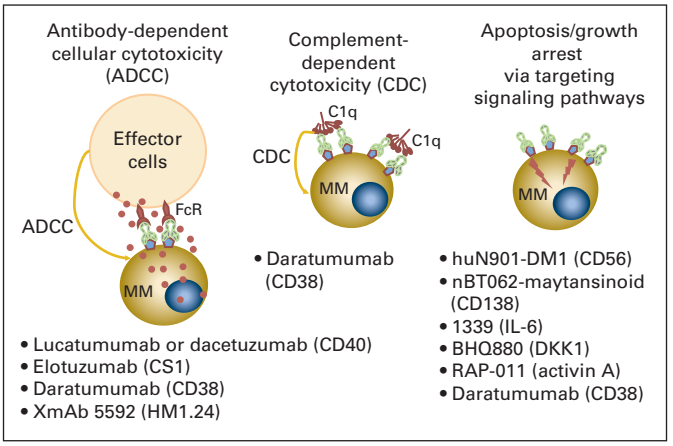

Fig 1. Monoclonal antibody therapeutic targeting of multiple myeloma (MM). Monoclonal antibodies evaluated in clinical trials mediate antibody-dependent cellular cytotoxicity (ADCC) or complement mediated cytotoxicity (CDC) as well as directly target growth or apoptotic signaling pathways. IL, interleukin. Data adapted.[12]

Our more recent focus in immune therapies has been on the development of vaccines. Vasair et al[15] have shown in murine MM and Rosenblatt et al[16] in human MM that vaccination with fusions of dendritic cells (DCs) with tumor cells allows for generation of T- and B-cell tumor–specific responses in vitro and in vivo preclinical models; derived recent clinical trials of MM-DC vaccinations to treat minimal residual disease posttransplantation are triggering host antitumor T-cell and humoral responses associated with high rates of complete response. An alternative strategy is the use of cocktails of peptides for vaccination. Specifically, we have shown that CS-1, XBP-1, and CD138 are functionally significant targets in MM cells and derived peptides from these antigens, which can be presented and trigger cytotoxic T lymphocyte responses in human leukocyte antigen A2–positive patients.[17] Ongoing clinical trials are evaluating vaccination with cocktails of these peptides in patients most likely to respond, with the goal of triggering immune responses with clinical significance.

We have also characterized the underlying immunodeficiency in patients with MM to design strategies to overcome it.[18] Our studies have demonstrated decreased help, increased suppression, pro-MM growth cytokines, and dysregulated immune-homeostasis, always with a view toward mechanism and clinical application. For example, the demonstration of increased TH-17 cytokines promoting MM cell growth set the stage for a related clinical trial of anti–interleukin-17 MoAb in MM.[18] In our studies of host accessory cells, we have shown that plasmacytoid DCs (pDCs) in patients with MM do not induce immune effector cells, as do normal pDCs, but instead promote tumor growth, survival, and drug resistance.[19] In preclinical studies, maturation of pDCs with CpG oligonucleotides both restores immune stimulatory function of pDCs and abrogates their tumor-promoting activity, setting the stage for a derived clinical trial.

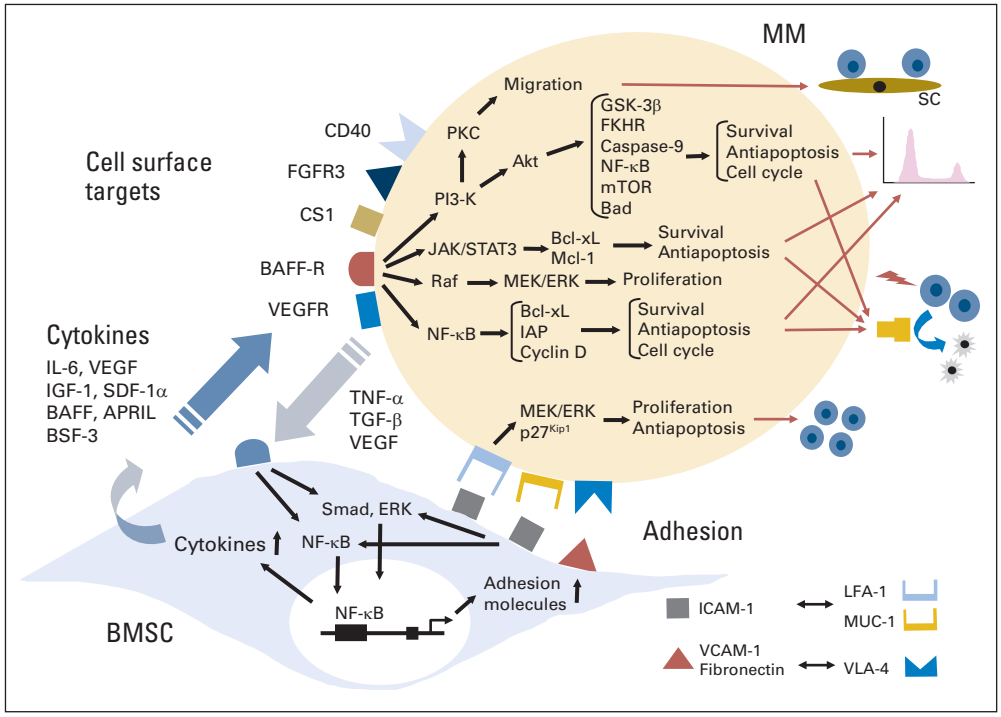

Fig 2. Targeting growth, survival, and drug resistance of multiple myeloma (MM) cells in the bone marrow microenvironment. Novel therapies can target the MM cell surface, cytokines, host-tumor cell interactions, and signaling pathways within tumor and accessory cells. APRIL, A Proliferation-inducing ligand; BAFF, B-cell activating factor; BAFF-R, B-cell activating factor receptor; BCL, B-cell lymphoma; BM, bone marrow; BMSC, bone marrow stromal cell; BSF, B-cell stimulating factor; FGFR, fibroblast growth factor receptor; FKHR, forkhead in human rhabdomyosarcoma; GSK, glycogen synthase kinase; IAP, inhibitor of apoptosis; ICAM, intercellular adhesion molecule; IGF, insulin-like growth factor; IL, interleukin; JAK, janus kinase; LFA, lymphocyte function-associated antigen; mTOR, mammalian target of rapamycin; MUC, mucin; NF-κB, nuclear factor κB; PKC, protein kinase C; SC, stromal cell; SDF, stromal cell–derived factor; STAT3, signal transducer and activator of transcription 3; TGF, transforming growth factor; TNF, tumor necrosis factor; VCAM, vascular cell adhesion molecule; VEGFR, vascular endothelial growth factor receptor; VLA, very late antigen. Data adapted.[1]

THERAPIES TARGETING THE TUMOR IN ITS MICROENVIRONMENT

From the 1990s to the present, we have developed in vitro and in vivo models to define the role of MM-BM interactions in pathogenesis, identify novel targets, and validate novel targeted therapies. We have then gone on to translate multiple single and combination agents targeting the tumor and microenvironment from bench to bedside in clinical trials. We have also used oncogenomics to characterize pathogenesis, identify novel targets, predict response, and inform design of single-agent and combination clinical trials.

Specifically, we have developed models of MM in the BM microenvironment that have been useful in defining the role of tumor cell–BM accessory cell contact as well as cytokines in the BM milieu in conferring growth, survival, and drug resistance in MM[1,20,21] (Fig 2). Importantly, these models have allowed for the identification of agents that can overcome cell adhesion–mediated drug resistance to conventional therapies. The proteasome inhibitor bortezomib, for example, triggers MM cell cytotoxicity in the BM, whereas antitumor activity of dexamethasone is completely attenuated.[22] Both at gene transcript and proteasome activity levels, the ubiquitin proteasome cascade is upregulated by MM-BM binding, perhaps contributing to its enhanced activity in this context.[23] Bortezomib directly targets chymotryptic proteasome activity, inhibits growth and survival, induces apoptosis, upregulates heat shock proteins, inhibits DNA damage repair, and induces endoplasmic reticulum stress in MM cells; downregulates adhesion molecules on tumor and BM, thereby abrogating adhesion; and, importantly, targets the microenvironment to trigger antiangiogenesis as well as apoptosis of osteoclasts while promoting osteoblast differentiation.[22,24-28] It was rapidly translated from the bench to the bedside and received accelerated US Food and Drug Administration approval in 2003 for treatment of relapsed refractory MM, followed by approval for relapsed MM and as initial therapy based on its superiority in randomized phase III clinical trials.[29-31] Most recently, promising data supporting bortezomib as consolidation and maintenance therapy have been emerging.

However, not all MMs respond to bortezomib, and some tumors ultimately develop resistance. From the outset, we have therefore tried to identify gene signatures of response versus resistance to bortezomib in MM[32] as well as develop functional assays to better predict patients whose cancers are most likely to respond. For example, we developed a predictive model in which tumors like MM with high proteasome load and low proteasome capacity have high proteasome stress and are therefore susceptible to proteasome inhibition, whereas solid tumors with high proteasome capacity and low proteasome load are relatively resistant to proteasome inhibitors.[33] Importantly, bortezomib has opened a whole new area of preclinical and clinical experimentation in cancer targeting the ubiquitin proteasome cascade upstream of the proteasome with deubiquitinating inhibitors, selectively or more broadly targeting proteasome activity, and targeting the immunoproteasome (Fig 3). For example, our preclinical studies show that inhibitors of deubiquitinating enzymes upstream of the proteasome, such as USP-7 inhibitor P5091, inhibit human MM cell growth, and prolong host survival in a murine xenograft model. Carfilzomib, a next-generation, more potent intravenous inhibitor of chymotryptic activity, can overcome bortezomib resistance in preclinical and early clinical trials. Oral proteasome inhibitors targeting chymotryptic activity that have translated from the bench to bedside in phase I clinical trials include Onyx 0912, which triggers cytotoxicity against MM cell lines and patient cells, and MLN2238/9708, which has shown more potent preclinical activity against MM cells in vivo than bortezomib.[34-39] NPI-0052 targets chymotryptic, tryptic-like, and caspase-like activities and similarly shows clinical promise.[38] Finally, inhibitors of the immunoproteasome, such as the PR-924 inhibitor of

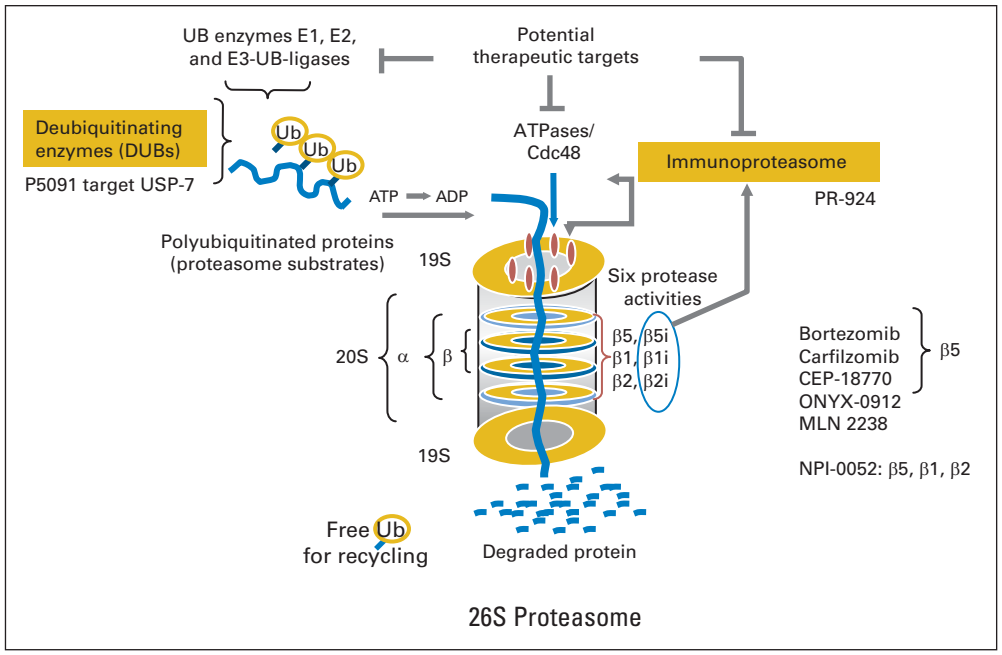

Fig 3. Proteasome: present and future therapies. Novel strategies of inhibiting the ubiquitin (UB) proteasome cascade include deubiquitinating enzyme inhibitors upstream of the proteasome; selective or broader inhibitors of the chymotryptic, tryptic, and caspase-like activities; and immunoproteasome inhibitors. USP, UB-specific peptidase.

the LMP-7 immunoproteasome subunit, also block MM growth in vitro and in vivo.[40]

Since the empiric observation that thalidomide had anti-MM activity in 1998, we have studied the IMiDs thalidomide, lenalidomide, and pomalidamide in our models of MM in the BM microenvironment. These agents directly trigger caspase 8–mediated apoptosis; decrease binding of tumor cells to BM; inhibit constitutive and MM cell binding–induced secretion of cytokines from BM; inhibit angiogenesis; and stimulate autologous natural killer, T, and natural killer–T cell immunity to MM cells.[41-43] Like bortezomib, lenalidomide was rapidly translated from the bench to the bedside. Our preclinical studies demonstrated increased responses when lenalidomide (which triggers caspase 8–mediated apoptosis) was combined with dexamethasone (which induces caspase 9–mediated apoptosis), and our phase I and II clinical trials both established the maximum-tolerated dose and confirmed the enhanced clinical efficacy of combined lenalidomide with dexamethasone, informing the design of phase III clinical trials leading to its US Food and Drug Administration/European Medicines Agency approval to treat relapsed MM.[29,30,44-48] Trials of lenalidomide as initial therapy in both transplantation candidate and elderly populations, as well as consolidation and maintenance therapy, are promising.[49,50] For example, maintenance lenalidomide has been shown to add years of progression-free survival in both newly diagnosed transplantation and nontransplantation candidates, further improving patient outcome. More recently, we and others have shown that the second-generation IMiD pomalidamide achieves remarkable and durable responses, with a favorable adverse effect profile, even in the setting of MM resistant to lenalidomide and bortezomib.[51,52]

THERAPIES TARGETING ACCESSORY CELLS WITH ANTI-MM ACTIVITY

Bortezomib and lenalidomide are examples of targeting the tumor and also affecting the microenvironment, because both positively affect bone disease in MM.[28,53] Conversely, we have also had a long-term interest in targeting the MM BM microenvironment, with the goal of also triggering MM responses (Fig 4). For example, MM cells secrete DKK-1, which downregulates osteoblast function via targeting Wnt signaling. In our preclinical murine xenograft models of human MM, the neutralizing anti–DKK-1 BHQ880 MoAb not only triggers new bone formation but also inhibits MM cell growth,[55] and a derived clinical trial of BHQ880 MoAb is ongoing. We have also shown that B-cell activating factor is elevated in the BM plasma of patients with MM and mediates osteoclastogenesis as well as tumor cell survival and drug resistance; importantly, anti–B-cell activating factor MoAb can neutralize these effects,[56] and a related clinical trial is ongoing. Most recently, targeting BTK in our preclinical models has not only blocked osteoclast formation and growth, thereby maintaining bone integrity, but also inhibited MM cell growth. These studies illustrate the principle that targeting cytokines or accessory cells in the tumor microenvironment can also affect MM cell growth, further validating the utility of our in vitro and in vivo model systems.

PRECLINICAL STUDIES TO INFORM COMBINATION TARGETED THERAPIES

We have also used functional oncogenomics to inform the design of novel combination therapies. For example, bortezomib was shown to inhibit DNA damage repair in vitro,[26] providing the rationale for its combination with DNA damaging agents to enhance or overcome drug resistance. Indeed, a large randomized phase III clinical trial of bortezomib versus bortezomib with pegylated doxorubicin showed prolonged progression-free and overall survival as well as increased extent and frequency of response,[57] leading to the US Food and Drug Administration approval of bortezomib with pegylated doxorubicin to treat relapsed MM. In a second example, we found heat shock protein 27 (Hsp 27) to be increased at transcript and protein levels in patient MM cells in the setting of bortezomib refractoriness. Our bedside-back-to-bench studies showed that overexpression of Hsp 27

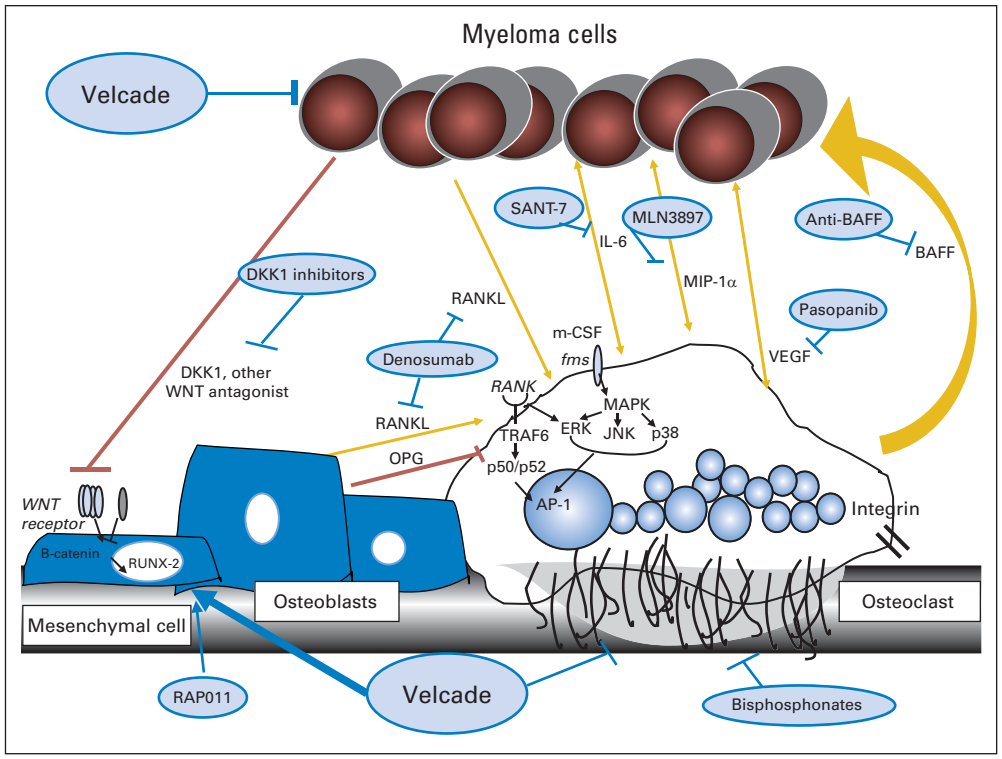

Fig 4. Targeting accessory cells in the multiple myeloma (MM) bone marrow microenvironment. Novel agents targeting cytokines mediating MM bone disease can also inhibit MM cell growth. BAFF, B-cell activating factor; IL, interleukin; JNK, c-Jun N-terminal kinase; MAPK, mitogen-activated protein kinase; m-CSF, macrophage colony-stimulating factor; MIP, macrophage inflammatory protein; OPG, osteoprotegerin; RANKL, receptor activator of nuclear factor κB ligand; RUNX, runt-related transcription factor; SANT, super antagonist; TRAF, tumor necrosis factor receptor–associated factor; VEGF, vascular endothelial growth factor. Data adapted.[54]

conferred bortezomib resistance, whereas knockdown of Hsp 27 in bortezomib-resistant MM cells restored sensitivity.[58] Hideshima et al[59] then showed that p38 mitogen-activated protein kinase inhibitor decreased downstream Hsp 27 and thereby overcame bortezomib resistance in MM cell lines and patient cells, providing the rationale for a clinical trial of bortezomib and p38 mitogen-activated protein kinase inhibitor. Third, on the basis of hallmark cyclin D abnormalities in MM, Raje et al[60,61] have studied cyclin D kinase inhibitors, alone and in combination, in MM. Fourth, Ghobrial et al[62] have translated promising preclinical data of mammalian target of rapamycin inhibitor and bortezomib into derived clinical trials. Fifth, we showed that bortezomib triggers activation of Akt and that bortezomib with Akt inhibitor perifosine can sensitize or overcome resistance to bortezomib in preclinical models.[63] Our derived phase I and II trials of combination therapy showed durable responses even in the setting of bortezomib resistance, and a phase III clinical trial of bortezomib versus bortezomib with perifosine in relapsed MM is ongoing for US Food and Drug Administration approval. Sixth, we believe that protein homeostasis represents one of the most attractive novel therapeutic targets in MM (Fig 5). Specifically, we have shown that inhibition of the proteasome upregulates aggresomal degradation of protein and, conversely, that blockade of aggresomal degradation induces compensatory upregulation of proteasomal activity.[66] Most importantly, blockade of aggresomal and proteasomal degradation of proteins by histone deacetylase (HDAC) inhibitors (eg, vorinostat, panibinostat, tubacin) and proteasome inhibitors (eg, bortezomib, carfilzomib), respectively, triggers synergistic MM cell cytotoxicity in preclinical studies.[64,66,67] We are leading international phase I and II clinical trials combining HDAC inhibitors vorinostat or panibinostat with bortezomib, which have achieved responses in the majority of patients with relapsed bortezomib-refractory MM, as well as phase III clinical trials for US Food and Drug Administration registration of these combinations. Excitingly, an HDAC 6 selective inhibitor causes acetylation of tubulin and more potently and selectively blocks aggresomal protein degradation; it mediates synergistic MM cytotoxicity when combined with bortezomib. This combination has been rapidly translated from our laboratory to the bedside, and clinical trials have been directed to achieve clinical efficacy without the adverse effect profile of fatigue, diarrhea, thrombocytopenia, and cardiac abnormalities attendant to the broader types 1 and 2 HDAC inhibitors.

To date, the most exciting combination from our preclinical studies is derived from the synergistic cytotoxicity induced by combined lenalidomide (caspase 8–mediated apoptosis) and bortezomib (caspase 9–mediated apoptosis) in models of MM cells in the BM milieu.[68] Richardson et al[69] led efforts to translate these findings into clinical trials in advanced MM, which showed that lenalidomide, bortezomib, and dexamethasone achieved 58% responses in relapsed refractory MM, often refractory to either agent alone. Most importantly, our center has shown that lenalidomide, bortezomib, and dexamethasone combination therapy for newly diagnosed MM achieves 100% responses, with 74% at least very good partial and 52% complete or near-complete responses.[46] Given these unprecedented results, a clinical trial is now evaluating whether high-dose therapy and stem-cell transplantation adds value in the context of this high extent and frequency of response to combined novel therapies. Therefore, the integration of combination novel-agent therapy, predicated on scientific rationale, is transforming the treatment paradigm in MM. Going forward, on the basis of these exciting results, we are now carrying out high-throughput drug screening to identify novel agents active against MM cells bound to BM stromal cells reflective of their microenvironment.

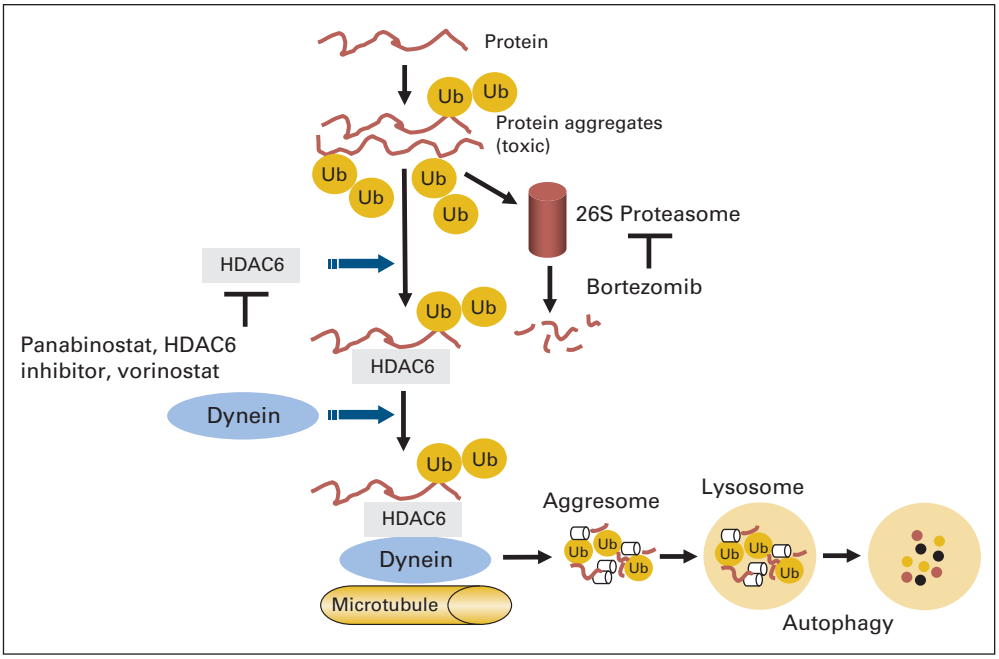

Fig 5. Blockade of ubiquitinated protein catabolism. Blockade of proteasomal and aggresomal breakdown using bortezomib and histone deacetylase (HDAC) inhibitors (panobinostat, vorinostat, HDAC6 selective inhibitor) mediate synergistic multiple myeloma cell cytotoxicity. UB, ubiquitin. Data adapted.[64-66]

ONCOGENOMIC STUDIES

From the 1990s to the present, we have used oncogenomics to characterize MM pathogenesis, identify novel targets, predict response, and inform the design of single-agent and combination clinical trials. Our earliest studies profiled transcriptional changes occurring with transition from normal plasma cells to monoclonal gammopathy of undetermined significance to MM as well as identified gene and protein changes distinguishing patient MM cells from normal plasma cells in a syngeneic twin.[70] We have repeatedly used transcript profiling to identify signatures of response, initially with bortezomib and subsequently with multiple other single and combination therapies,[32] and most recently shown that microRNA profiling can also identify prognostic subgroups. Our DNA-based array comparative genomic hybridization studies have identified copy number alterations (CNAs) and suggested novel MM oncogenes or suppressor genes; once validated using knock-in and knockdown experiments in our models of MM cells in the BM milieu, these may serve as potential therapeutic targets[71] (Fig 6).

Single nucleotide polymorphism array has also identified CNAs and allowed for the development of novel prognostic models.[72] For example, recent single nucleotide polymorphism analyses of clinically annotated samples have identified CNAs, including increased 1q and 5q as sites for putative MM oncogenes as well as decreased 12p as a site of putative MM suppressor genes, to predict for clinical outcome.[72] Most importantly, as one of the founding centers of the Multiple Myeloma Research Consortium, we have participated in MM genome sequencing studies that have revealed mutated genes involved in protein homeostasis, nuclear factor κB signaling, IRF4 and Blimp-1, and histone methylating enzymes, all consistent with MM biology.[73] These studies have also identified unexpected mutations, such as those in *BRAF* observed in melanoma, which may have short-term clinical application. Finally, our early studies now show continued evolution of genetic changes with progressive MM, strongly supporting the view that personalized medicine in MM must include profiling patient tumor cells not only at diagnosis but also at time of relapse.

FUTURE DIRECTIONS AND CONCLUSIONS

Our ongoing efforts include the development of immune (vaccine and adoptive immunotherapy) strategies, development of novel agents targeting the MM cell in the BM microenvironment, development of rationally based multiagent combination therapies, and use of

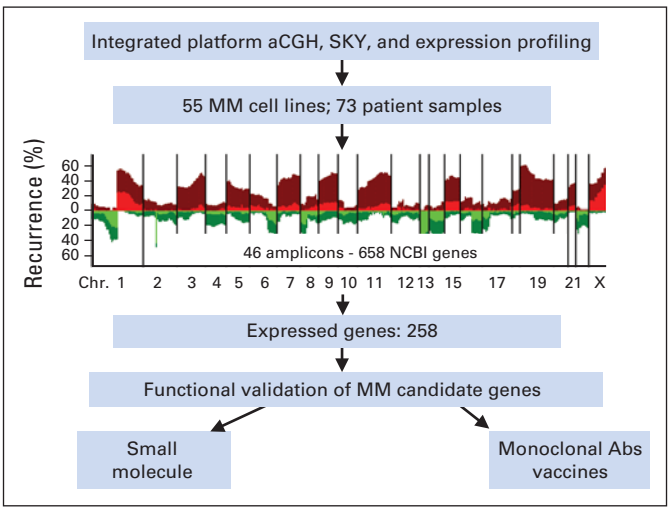

Fig 6. Oncogenomics to identify targeted therapies. Array comparative genomic hybridization (aCGH) of multiple myeloma (MM) cell lines and patient samples identifies amplicons with putative MM oncogenes. Profiling identifies transcribed genes, which are then functionally validated in overexpression and knockdown experiments in MM cells in the bone marrow microenvironment. Validated cell surface molecules can be targeted with monoclonal antibodies (Abs) or vaccines, whereas intracellular molecules are targeted with small molecule inhibitors. NCBI, National Center for Biotechnology Information; SKY, spectral karyotyping. Data adapted.[71]

genomics to improve both patient classification and allow for personalized medicine in MM. With this continued rapid evolution of progress, MM will be a chronic illness with sustained complete responses in a significant fraction of patients.

In closing, I want to gratefully acknowledge the laboratory and clinical researchers at our center and throughout the world with whom I have had the privilege to work over many years. Not only have we together had an impact on the natural history of MM, but the next generation of leaders in MM research is now in place to expedite progress even further. We not only share academic interests in MM but also treasure longstanding personal friendships. I am deeply grateful to the many funding organizations and individuals supporting our efforts over many years. None of this would have been possible without the loving support of my family. And most importantly, I have been honored to care for many extraordinary patients, who are truly my heroes and will always be the inspiration for all that we do.

AUTHOR'S DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

Although all authors completed the disclosure declaration, the following author(s) indicated a financial or other interest that is relevant to the subject matter under consideration in this article. Certain relationships marked with a "U" are those for which no compensation was received; those relationships marked with a "C" were compensated. For a detailed description of the disclosure categories, or for more information about ASCO's conflict of interest policy, please refer to the Author Disclosure Declaration and the Disclosures of Potential Conflicts of Interest section in Information for Contributors.

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JOURNAL OF CLINICAL ONCOLOGY

SPECIAL SERIES OVERVIEW

Caring for the Whole Patient: The Science of Psychosocial Care

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Jimmie C. Holland, *Memorial Sloan-Kettering Cancer Center, New York, NY*
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This *Journal of Clinical Oncology* Special Series relates to the science of psychosocial care. This series is designed to provide oncology professionals with the most recent information about the psychological, psychiatric, and social aspects of cancer care. The emergence of the field of psychosocial care reflects growing public and professional awareness of the potential for cancer and its treatment to have profound effects on many aspects of life. A principal goal of psychosocial care is to recognize and address the effects that cancer and its treatment have on the mental status and emotional well-being of patients, their family members, and their professional caregivers. In addition to improving emotional well-being and mental health,[1] provision of psychosocial care has been shown to yield better management of common disease-related symptoms and adverse effects of treatment, such as pain[2] and fatigue.[3]

Given the centrality of psychosocial issues in cancer, it is surprising that the formal history of this field in the United States dates only to the 1970s.[4] This relatively late development becomes more understandable when one realizes that only then had the stigma attached to cancer diminished to the extent that most patients were told their diagnosis, thus making it possible to openly study psychosocial issues.[4] A second factor contributing to the field's late development is the stigma attached to mental illness and psychological problems, even in the context of medical illness.[4] During the last 40 years, a subspecialty devoted to cancer-related psychosocial care (ie, psycho-oncology) has become firmly established, with its own journals, scientific meetings, and professional societies.

Psychosocial care in oncology received increased attention after the publication in 2008 of an Institute of Medicine (IOM) report entitled, "Cancer Care for the Whole Patient: Meeting Psychosocial Health Needs."[5] This report reflects the work of a multidisciplinary panel that sought to evaluate how best to translate research findings about psychosocial care into practical applications for the purpose of improving the quality of cancer care. The panel found evidence for the effectiveness of an array of formal psychosocial services including counseling and psychotherapy, pharmacologic management of mental symptoms, illness self-management and self-care programs, family and caregiver education, and health promotion interventions. The panel also found that, despite this evidence, many individuals who could benefit from these services do not receive them.

The editors of this *JCO* Special Series on psychosocial care have chosen a number of topics that illustrate recent advances in this important area. The remainder of this overview will place these topics into clinical context, and the reader is encouraged to refer to the individual articles contained in this Special Series for additional details.

Jacobsen and Wagner[6] describe three important developments in recent years that have the potential to greatly increase the numbers of patients who receive needed psychosocial care. One development has been the formulation of standards of cancer care by the IOM panel and a number of professional organizations and accrediting bodies that include the psychosocial component of care.[7-9] A second development has been the issuance of clinical practice guidelines by the National Comprehensive Cancer Network (NCCN) and other organizations that include specific recommendations for the psychosocial care of patients with cancer.[10-12] A third development has been the formulation and implementation of measurable indicators of the quality of psychosocial care in oncology settings, including those used as part of the American Society of Clinical Oncology's Quality Oncology Practice Initiative.[13]

NCCN was among the first organizations to propose guidelines related to psychosocial care. These guidelines, first issued in 1999, focus on the recognition and management of distress in patients with cancer.[12] As noted by Carlson et al,[14] the rationale for focusing on distress, even though it is not a precise clinical term, is that it is easily understood by the lay person and does not carry the stigma that is often associated with more formal psychiatric terminology. The authors identify a number of brief self-report measures of distress and unmet needs that can be used in combination to identify distressed patients as well as possible sources of distress in these patients that can be targeted for intervention.[14] Although NCCN guidelines recommend routine screening for distress,[12] there has been limited research that evaluates whether implementation of distress screening programs leads to better outcomes. Evidence to date suggests that screening can improve communication between patients and clinicians and increase psychosocial referrals but is inconclusive with respect to the effects on quality of life and other patient-reported outcomes.[14]

Fann et al[15] describe a different approach to the delivery of integrated psychosocial care that is based on the collaborative care model of depression that is found to be effective in primary care settings.[16] Key elements of this approach include implementation of depression screening to identify patients with depression, use of evidence-based protocols for treatment of depression, structured collaborations between primary medical providers and mental health

specialists, and active monitoring of adherence to depression treatment and outcomes.[17] Several randomized trials have now demonstrated that this approach is both feasible and effective for treating depression in patients with cancer.[18,19] Building on this evidence, the authors identify several ways in which the collaborative care model could be adapted to address other important psychosocial issues in oncology settings, such as health promotion.[15]

The availability of a sound evidence base is central to efforts to develop integrated models of psychosocial care delivery. As reviewed by Li et al,[20] research on the pharmacologic management of depression in patients with cancer is limited; consequently, treatment guidelines must be derived in part from research in psychiatric and nononcology medical populations. Investigators have conducted considerably more research on the use of psychosocial interventions in the management of depression in patients with cancer. Taken together, findings in this area suggest that a multicomponent approach is likely to be most effective, with psychosocial interventions being tailored to the severity of depression and the stage of disease, and combined with pharmacotherapy for more severe forms of depression.[20] The review by Traeger et al[21] yields similar conclusions with respect to the management of anxiety in patients with cancer. Delirium is another example of a psychosocial issue for which an integrated care delivery model requires a sound research base. As reviewed by Breitbart and Alici,[22] there have been an increasing number of delirium treatment studies as well as prevention studies published in recent years. The evidence most clearly supports the short-term, low-dose use of antipsychotic medications for control of delirium symptoms.[22] There is also evidence for the benefits of assessing and modifying key clinical factors that can precipitate delirium (eg, pain, sleep disturbance, and poor nutrition).[22]

Stimulated in part by a 2006 IOM report that identified important gaps in the care of cancer survivors,[23] the period after the completion of cancer treatment is now a major focus of psychosocial care. This development is consistent with the IOM report's view that the essential components of survivorship care include intervention for the consequences of cancer treatment.[23] Among the longer-term consequences of cancer diagnosis and treatment that were identified in the IOM report are several that can be addressed through psychosocial care (eg, emotional distress, sexual dysfunction, and employment and insurance concerns).[23] Stanton[24] highlights the importance of providing psychosocial care during the re-entry phase of cancer survivorship—that is, in the several months immediately after treatment completion. Patients' psychosocial concerns are likely to be heightened during this period because of perceptions that they have lost the safety net of active treatment and because of challenges faced in resuming or altering former occupational and social roles.[24]

Adolescents and young adults experience a separate set of challenges as a result of the disruptive impact that cancer and its treatment can have on normal developmental transitions in this age group. Zebrack and Isaacson[25] identify several ways in which psychosocial care during and after cancer treatment needs to be tailored to the unique needs of the adolescent and young adult population.

As noted previously, the scope of psychosocial care extends beyond the patient to encompass family members and professional caregivers. Among family members, addressing the psychosocial needs of those who participate in the patient's care is particularly important. With cancer treatment moving increasingly into the outpatient setting, family members are being asked to take on greater responsibilities for patient care. Northouse et al[26] review evidence that indicates that the stress of caregiving can have a strong negative impact on the health and well-being of the family caregiver. These reactions, in turn, can have a negative impact on the caregiver's ability to provide needed care and on the ill family member's health and well-being. Conversely, psychosocial intervention research indicates that when the caregiver/patient dyad is treated as the unit of care, important synergies are achieved that contribute to the well-being of both.[26] The current challenge, as outlined by the authors, is to incorporate this intervention approach into routine clinical practice. Among the barriers that need to be addressed are the lack of professional awareness of caregivers' needs, the lack of professional training in how to intervene with caregivers, and concerns that caregiver interventions are too costly to implement.[26]

Caring for patients with cancer can also exact a psychological toll on oncologists. One of the most common manifestations of distress in professional caregivers is burnout, a syndrome that is characterized by a loss of enthusiasm for work, cynicism, and a low sense of personal accomplishment.[27] Shanafelt and Dyrbye[28] cite evidence that suggests that 25% to 38% of oncologists are experiencing burnout at any given point in time. Among the many possible causes of burnout, high workload, inefficiency, loss of autonomy, and lack of meaning in work are central factors.[28] Additional factors that are relevant to the practice of oncology include being faced with making life and death decisions on a frequent basis, administering highly toxic therapies with narrow therapeutic windows, having limited ability to prolong life in many patients, and needing to keep up with the rapid pace of scientific and treatment advances.[29,30] Systematic research into ways to prevent burnout among physicians is still in an early stage of development. Preliminary evidence suggests that a mix of organizational strategies that address workplace issues and personal strategies that promote wellness and enhance the meaning derived from professional activities merit additional evaluation.

Receiving training in communication skills may be another means for oncologists to improve their professional lives. Beyond its potential role in reducing work-related stress, communicating well with patients has been linked to greater satisfaction and reduced anxiety among patients, better patient health outcomes, and fewer malpractice claims.[31] Kissane et al[32] review evidence that demonstrates that providing oncology clinicians with formal training in skills for communicating with patients has a strong positive impact on their communication behaviors. On the basis of the evidence, they argue that communication skills training should be a standard part of oncology training programs, and they outline a core curriculum that cover topics such as how to discuss prognosis at each illness phase and how to promote shared decision making in the selection of anticancer treatments.

The 11 articles in this Special Series demonstrate the depth and breadth of the science that underlies the psychosocial care of people who are affected by cancer. Although important gaps in research still exist, work in this area has evolved to the extent that evidence-based recommendations can be formulated for many frequently encountered psychosocial issues. A common theme in many of the articles, however, is the continuing need to translate research findings into clinical practice, given that psychosocial care still does not reach many who could benefit from it. The growing trend for psychosocial care to

be included in standards for quality cancer care represents an important step toward its greater availability and routine use. Our hope is that this Special Series will also contribute to this goal by promoting greater knowledge and understanding of psychosocial care among oncology professionals.

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COMMENTS AND CONTROVERSIES

Cancer Survivorship and Cancer Rehabilitation: Revitalizing the Link

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Increasing national attention focuses on the specialized needs of disease-free survivors of cancer.[1-5] This is a direct reflection of the growing number of survivors of cancer in the US, currently estimated at almost 12 million,[6] and the many challenges of delivering optimal health care to these individuals. The health system will be further stressed by the aging of the US population during the next 25 years and the corresponding increase in long-term survivors. Most cancers are diagnosed in older adults who have preexisting comorbid conditions that are exacerbated by cancer treatment. The convergence of preexisting and new chronic conditions in older survivors of cancer is a major challenge for health care policy and delivery. To meet this challenge, we must develop a model of care delivery to maximize the health and well-being of survivors of cancer, focusing on effective symptom management, prevention of late effects, and health promotion. It is time to revitalize the link between cancer survivorship and cancer rehabilitation and investigate a new model of comprehensive cancer rehabilitation, involving a multidisciplinary team of providers that aims to optimize the patient's physical, psychologic, vocational, and social functioning given the limits imposed by the chronic or late effects of cancer treatment and other comorbid conditions.

History of Cancer Rehabilitation in the United States

The National Cancer Act of 1971 launched an ambitious national research program to improve cancer diagnosis, treatment, and care delivery. It funded clinical cancer research centers and demonstration projects in the late 1970s to assess rehabilitation needs and implement and evaluate interventions to address these needs.[7-11] By the early 1980s, several well-established programs throughout the country provided rehabilitation services to patients with cancer.[9] These services were largely hospital-based, integrated with other rehabilitation services or oncology departments, and involved a multidisciplinary team of providers.[9]

What happened during the past 30 years to change this situation? In the 1980s, most cancer treatment occurred in tertiary, large-volume, specialized centers.[12] A combination of treatment advances, earlier detection, less radical surgery, use of combined-modality therapy, and prolonged outpatient adjuvant endocrine therapy reduced the length of hospital inpatient care; now the vast majority of oncology care occurs in practices that are physician-owned rather than hospital-based.[13]

The surgical management of breast cancer is illustrative. By the 1980s, the radical mastectomy was no longer being performed, thus reducing its related serious arm and shoulder morbidity. By the 1990s, breast conserving surgery was established as the preferred surgical treatment.[14] Increased diagnosis of small tumors detected by mammography led to even shorter breast surgery hospitalizations and limited or no axillary dissections, moving primary breast surgery to the outpatient arena. Thus, the extensive need for postmastectomy rehabilitation diminished, the opportunity for hospital-based rehabilitation was limited, and systematic delivery of postoperative rehabilitation virtually disappeared. Most women today do not receive the physical[15,16] and psychosocial[3] services that were so integral to those earlier rehabilitation programs. When cancer rehabilitation services are prescribed today, they tend to have a one-dimensional focus rather than comprehensive assessment and treatment of needs. For example, in a study of services offered by National Cancer Institute–designated comprehensive cancer centers, 70% of centers had a lymphedema management program, but no comprehensive cancer rehabilitation programs were reported.[17] In the ≥ 30 years of experience of the authors (P.G. and J.R.), similar patterns have occurred for other common cancers (lung, colorectal, bladder, head and neck, and gynecologic).

Changing Patterns of Cancer Care Delivery

Changes in US cancer care delivery toward a community-based delivery system have exacerbated the disconnect between cancer survivorship and cancer rehabilitation.[13] With less complex surgical treatments and prolonged adjuvant chemotherapy, traveling long distances to a tertiary center became undesirable, and community cancer centers were established. Community standards for cancer care were established and fostered by the American College of Surgeons and its hospital certification programs.[18] The National Cancer Institute contributed to the decentralization of cancer care by enabling the widening group of community practitioners to offer their patients access to clinical trials through its Community Clinical Oncology Program.[19,20]

Despite delivering high-quality cancer care in the community, the dissemination of cancer rehabilitation services into this setting has been limited. Poor integration of these services into current tertiary center treatment programs, where trainees lack exposure to rehabilitation services and appreciation of their added value, limits uptake and provision of these services when these oncologists ultimately join community practices or hospitals. Fragmentation of cancer care in the community setting further exacerbates this problem. Although the hospital is a focal point for surgery and radiation, most medical oncology care is delivered in private office settings, and there is no common electronic medical record allowing all providers caring for the patient to communicate about the patient's needs. Finally, as discussed by others, cancer care and rehabilitation care are disconnected even in some institutions that have both services,[15,21,22] and many community settings lack rehabilitation care altogether.

Financing of Health Care and Rehabilitation Services

Despite the potential benefits of outpatient cancer rehabilitation services, accessing this care entails navigating multiple barriers. The diversity of health insurance coverage with its broad mix of payers and numerous plan types has complicated authorization and reimbursement. Most rehabilitation services are fully or partially covered through the majority of insurance plans. For example, Medicare offers coverage for rehabilitation services such as physical and occupational therapy in the community outpatient setting. However, the limited coverage schedule, funding caps, and strict guidelines for continuation of therapy may mean that some survivors of cancer cannot receive their recommended therapy. Private health insurers are mandated to cover physical and occupational therapy services in some states,[23] but coverage for these services can vary widely and have substantial copays that discourage the financially stressed survivor of cancer. Finally, accessing rehabilitation services is dependent on referral and the ability of providers and administrative staff to understand and work with health insurance plans to obtain services. Providers must be able to ensure timely preauthorizations and prescriptions for continuation of services, locate high-quality in-network providers, understand referral processes, and assist patients in making sense of complex benefit schedules. At present, the existing patchwork of state and federal mandates, complex benefits schedules, and variable patient cost sharing among health insurance plans may be contributing to the underuse of cancer rehabilitation services.

Needs of Survivors of Cancer Today

The multidisciplinary team approach central to comprehensive cancer rehabilitation is ideal for meeting the needs of survivors of cancer. First, it assesses and treats the chronic effects of cancer and prevents or mitigates the effects of late-occurring sequelae. Depending on the specific treatment exposures, survivors of cancer can face numerous adverse consequences of cancer treatment, many of which are amenable to rehabilitation interventions. These include fatigue, depression, anxiety, fear of recurrence, cognitive dysfunction, pain syndromes, peripheral neuropathy, sexual dysfunction, balance and gait problems, upper or lower quadrant mobility issues, lymphedema, bladder and bowel problems, stoma care, problems with swallowing or dysphagia, and communication difficulty.[24] Although other models of care assess and treat these problems, the team in the comprehensive rehabilitation model evaluates the sum total of problems that a survivor faces and coordinates treatment. Second, comprehensive cancer rehabilitation can address pre-existing or treatment-related comorbid conditions. Diabetes, cardiovascular disease, congestive heart failure, bone loss, adverse body composition, and renal disease are common in survivors of cancer[1] and can be managed through rehabilitation interventions including medication, counseling, behavior change and promotion of healthy diets, physical activity, and weight control.[24] Third, self-management skills and health promotion interventions provided in the context of comprehensive cancer rehabilitation also have the potential to decrease the risk of additional late effects—for example, the cardiac, pulmonary, endocrine, or bone complications of cancer treatment[24] and may even reduce the risk of second malignancies.[25-31] A final benefit is the joint focus on optimizing functional status and quality of life, preserving the ability to remain in the workforce[32] and other life roles, and maximizing health and longevity.

A Call to Build a Better Model of Cancer Rehabilitation: Can We Make It Work for Survivors?

The crisis in cancer care presents a challenge and an opportunity. We must identify a new model of survivorship care that is responsive to the needs of the growing number of survivors of cancer and can be effectively delivered within the evolving health care system. We suggest that a coordinated, comprehensive cancer rehabilitation model provides many conceptual advantages including treating chronic and late effects of cancer, managing comorbid conditions, and focusing on prevention. Varied forms of this approach are used in several Nordic and European countries,[33] whereas Italy[34] and the United Kingdom[35] are currently studying or piloting programs. However, despite the international support for a comprehensive approach, long-term effectiveness data on this model are lacking.[33]

In addition to considering these programs from other countries, our efforts to build a better model of comprehensive cancer rehabilitation can be informed by several existing US rehabilitation models. One possibility is to adapt the existing cardiopulmonary rehabilitation model consisting of exercise training and other services as needed, usually coordinated by an exercise specialist, as has been suggested by Schmitz.[36] Alternatively, we could adapt the current model of rehabilitation from trauma (eg, spinal cord injury, traumatic brain injury) involving a broader network of multidisciplinary providers and coordinated by a physiatrist. Either of these models would have to be adapted to the needs of survivors of cancer and responsive to survivors with extensive as well as minor rehabilitation needs.

A new comprehensive model needs to be tested against current, fragmented models of cancer rehabilitation services or other hybrid rehabilitation models. Comparative effectiveness studies can test whether a comprehensive cancer rehabilitation program yields improvements in patient, health care system, and cost outcomes. Once an appropriate model of care is identified, risk stratification models will be needed to determine how to identify and effectively refer survivors for rehabilitation services and then how to transition them back to primary care. Implementation research is needed to identify how to best deliver this model of care—for example, rehabilitation could be prescribed as part of survivorship care plans being implemented currently across the country and potentially mandated by the American College of Surgeons for hospital certification in the future. A renewed effort is required to demonstrate the benefit of rehabilitation services by using randomized trials as a step toward incorporating these services into the standard of care. Implementing cancer rehabilitation on a broad scale will require training more cancer rehabilitation providers and educating oncology and primary care providers

about the benefits of these services, including how to identify and refer survivors for this care. Building and implementing a better model of comprehensive cancer rehabilitation will require a coordinated strategic effort of research and policy change. With a sustained integrated approach, we have the potential to significantly enhance the quality and length of survival for current and future survivors of cancer.

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Demand more. With VELCADE® combined, 30 % of patients experienced a complete response compared with 4 % on melphalan-prednisone (MP) alone (p<0.001)[1]
VELCADE® plus melphalan-prednisone demonstrated a significantly greater overall survival of 68.5 % at 3 years (vs. 54 % with MP)[2]

VELCADE® provides superior rate of survival to dexamethasone at 1 year in relapsed-refractory disease (80 % vs. 66 %. p=0.003)[3], a superior overall survival (29.8 months vs. 23.7 months, p=0.027), and a better chance of complete response (9 % vs. <1 %)[4]
Overall and complete response rates with VELCADE® were 43 % and 9 %, respectively[4]

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References: 1. San Miguel JF, Schlag R, Khuageva NK, *et al.* Bortezomib plus Melphalan and Prednisone for Initial Treatment of Multiple Myeloma. *New England Journal of Medicine* 2008; **359**:906-917. **2.** Mateos M-V, Richardson PG, Schlag R, *et al.* Bortezomib Plus Melphalan and Prednisone Compared with Melphalan and Prednisone in Previously Untreated Multiple Myeloma: Updated Follow-Up and Impact of Subsequent Therapy in the Phase III VISTA Trial. *Journal of Clinical Oncology* 2010; **28**:2259-2266. **3.** Richardson PG, Sonneveld P, Schuster MW, *et al.* Bortezomib or High-Dose Dexamethasone for Relapsed Multiple Myeloma. *New England Journal of Medicine* 2005; **352**:2487-2498. **4.** Richardson PG, Sonneveld P, Schuster M, *et al.* Extended follow-up of a phase 3 trial in relapsed multiple myeloma: final time-to-event results of the APEX trial. *Blood* 2007; **110**(10):3557-3560. **5.** VELCADE® package insert (May 2011).